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Toxicological Profile for

LEAD

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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TOXICOLOGICAL PROFILE FOR LEAD

Prepared by:

Clement International Corporation
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Prepared for:

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

UPDATE STATEMENT

A Toxicological Profile for lead was released on June 1990. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
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FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987, on October 20, 1988, on October 26, 1989, on October 17, 1990, and on October 17, 1991. A revised list of 275 substances was published on October 28, 1992.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following:

(A) The examination, summary, and interpretation of available toxicological information and epidemiological evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

Foreword

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures the consistency with ATSDR policy.

2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying endpoints.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

4. Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about lead and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,300 sites on its National Priorities List (NPL). Lead has been found in at least 922 of these sites. However, we do not know how many of the 1,300 NPL sites have been evaluated for lead. As EPA evaluates more sites, the number of sites at which lead is found may change. This information is important for you to know because lead may cause harmful health effects and because these sites are potential or actual sources of human exposure to lead.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous chemical such as lead, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS LEAD?

Lead is a naturally occurring bluish-gray metal found in small amounts in the earth's crust. It has no characteristic taste or smell. Metallic lead does not dissolve in water and does not burn. Some natural and man-made substances contain lead, but do not look like lead in its metallic form. Some of these substances can burn.

Lead has many different uses. Its most important use is in the production of some types of batteries. Other uses include the production of ammunition, in some kinds of metal products (such as sheet lead, solder, and pipes) and in ceramic glazes. Some chemicals containing lead, such as tetraethyl lead and tetramethyl lead, are used as gasoline additives. However, the use of these lead-containing chemicals in gasoline is much less than it used to be because the last producer of these additives in the United States stopped making them in early 1991. Other chemicals containing lead are used in paint. The amount of lead added to paints and ceramic products, caulking, gasoline additives, and solder has also been reduced in recent years because of lead's harmful effects in humans and animals. However, the use of lead in ammunition and roofing has actually increased in recent years. Lead is also used for radiation shields for protection against X-rays and in a large variety of medical (electronic ceramic parts of ultrasound machines, intravenous pumps, fetal monitors, and other surgical equipment), scientific (circuit boards for computers and other electronic circuitry), and military equipment (jet turbine engine blades, military tracking systems).

Most lead used by industry comes from mined ores ("primary") or from recycled scrap metal or batteries ("secondary"). Human activities (such as use of "leaded" gasoline) have spread lead and substances that contain lead to all parts of the environment. For example, lead is in air, drinking water, rivers, lakes, oceans, dust, and soil. Lead is also in plants and animals that humans may eat. Please see Chapter 3 for more information on the physical and chemical properties of lead. Chapter 4 contains more information on the production and use of lead.

1.2 WHAT HAPPENS TO LEAD WHEN IT ENTERS THE ENVIRONMENT?

Lead occurs naturally in the environment. However, most of the lead dispersed throughout the environment comes from human activities. Before the use of leaded gasoline was limited, most of the lead released into the U.S. environment came from car exhaust. Since the EPA has limited the use of leaded gasoline, the amount of lead released into the air has decreased. In 1979, cars released 94.6 million kilograms (kg) of lead into the air in the United States. In contrast, in 1989 cars released only 2.2 million kg to the air. Other sources of lead released to the air include burning fuel, such as coal or oil, industrial processes, and burning solid waste.

The release of lead to air is now less than the release of lead to soil. Most of the lead in inner city soils comes from landfills and leaded paint. Landfills contain waste from lead ore mining, ammunition manufacturing, and from other industrial activities such as battery production. Very little lead goes directly into water.

Higher levels of lead from car exhausts can be measured near roadways. Very low levels of lead from car exhausts are found at distances of 25 meters (about 80 feet) from the road edge. However, once lead goes into the atmosphere, it may travel thousands of miles if the lead particles are small or if the lead compounds are volatile. Lead is removed from the air by rain as well as by particles falling to the ground or into surface water. Once lead deposits on soil, it usually sticks to soil particles. Small amounts of lead may enter rivers, lakes, and streams when soil particles are displaced by rainwater. Lead may remain stuck to soil particles in water for many years. Movement of lead from soil particles into underground water or drinking water is unlikely unless the water is acidic or "soft."

Some of the chemicals that contain lead are broken down by sunlight, air, and water to other forms of lead. Lead compounds in water may combine with different chemicals depending on the acidity and temperature of the water. The lead atom cannot be broken down.

The levels of lead may build up in plants and animals from areas where air, water, or soil are contaminated with lead. If animals eat contaminated plants or animals, most of the lead that they eat will pass through their bodies. It is the small amount absorbed that can cause harmful effects. Chapters 4 and 5 contain more information on the environmental fate of lead.

1.3 HOW MIGHT I BE EXPOSED TO LEAD?

People living near hazardous waste sites can be exposed to lead and chemicals that contain lead by breathing air, drinking water, eating foods, or swallowing or touching dust or dirt that contains lead. For people who do not live near hazardous waste sites, most exposure to lead occurs by eating foods that contain lead, occupationally in brass/bronze foundries, or in areas where leaded paints exist. Foods such as fruits, vegetables, meats, grains, seafood, soft drinks, and wine may have lead in them. Cigarettes also contain small amounts of lead. In general, very little lead is in drinking water. More than 99% of all drinking water contains less than 0.005 part of lead per million parts of water (ppm). However, the amount of lead taken into your body through drinking water can be higher in communities with acidic water supplies. Acidic water can make the lead found in lead pipes, solder, and brass faucets enter water. Eating lead-based paint chips or dust is another way you can be exposed to lead. These two latter routes are particularly relevant to children in lower-income urbanized populations. For occupationally exposed individuals, the predominant route of exposure is the inhalation of lead particles.

Exposure to gasoline additives that contain lead can happen while you are pumping leaded gasoline, from sniffing leaded gasoline, and possibly during the use of some do-it-yourself fuel additives. For people who are exposed to lead at work, the largest source of exposure comes from breathing air that contains lead. Breathing or swallowing dust and dirt that has lead in it is another way you can be exposed to lead. Children, especially those who are preschool age, can have a lot of lead exposure because they put many things into their mouths. Their hands, toys, and other items may have lead-containing dirt on them. In some cases, children swallow nonfood items such as paint chips and dirt ("pica"). These items may contain very large amounts of lead, particularly in and around older houses that were painted with lead-based paint. The paint in these houses often chips off and mixes with dust and dirt. Some old paint (when it is dry) is 5–40% lead. Skin contact with dust and dirt containing lead occurs every day. However, not much lead can get into your body through your skin. During normal use of lead-containing products, very little lead gets on your skin.

The burning of gasoline has been the single largest source (90%) of lead in the atmosphere since the 1920s. A lot less lead in the air comes from gasoline now because EPA reduced the amount of lead that can be used in gasoline. Less than 35% of the lead released to the air now comes from gasoline. Other sources of lead in the air include releases to the air from industries involved in iron and steel production, lead-acid-battery manufacturing, brass foundries, and manufacturing of tetraethyl and tetramethyl lead, the latter two being very volatile. Lead released into air may also come from burning of solid waste, windblown dust, volcanoes, exhaust from workroom air, burning or weathering of lead-painted surfaces, and cigarette smoke.

Sources of lead in drinking water include lead that can come out of lead pipes, faucets, and solder used in plumbing. Lead-containing plumbing may be found in public drinking water systems, in houses, apartment buildings, and public buildings. Sources of lead in surface water or sediment include deposits of lead-containing dust from the atmosphere, waste water from industries that handle lead (primarily iron and steel industries and lead producers), and urban runoff.

Sources of lead in food and beverages include deposition of lead-containing dust from the atmosphere on crops and during food processing and uptake of lead from soil by plants. Lead may also enter foods when foods are put into improperly glazed pottery and ceramic dishes and leaded-crystal glassware. Illegal whiskey made using stills that contain lead-soldered parts (such as truck radiators) may also contain lead. The potential for exposure to lead in canned food from lead-soldered containers is greatly reduced because the content of lead in canned foods has decreased 87% from 1980 to 1988. Lead may also be released from soldered joints in kettles used to boil water for beverages.

Sources of lead in dust and soil include deposition of atmospheric lead and weathering and deterioration of lead-based paint. Lead in dust may also come from windblown soil. Disposal of lead in municipal and hazardous waste dump sites also adds lead to soil.

Exposure to lead occurs in many jobs. People employed in lead smelting and refining industries, brass/bronze foundries, rubber products and plastics industries, soldering, steel welding and cutting operations, battery manufacturing plants, and alkyl lead manufacturing industries may be exposed to lead. People who work at gasoline stations, in construction work, and at do-it-yourself renovations, or who work at municipal waste incinerators, pottery and ceramics industries, radiator repair shops, and other industries that use lead solder may also be exposed. Between 0.5 and 1.5 million workers are exposed to lead in the workplace; in California alone over 200,000 workers are exposed to lead. Families of workers may be exposed to elevated levels of lead when workers bring home lead dust on their work clothes. You may also be exposed to lead in the home if you work with stained glass as a hobby, or if you are involved in home renovation that involves the removal of old lead-based paint. Chapter 5 contains further information on sources of exposure to lead.

1.4 HOW CAN LEAD ENTER AND LEAVE MY BODY?

Some of the lead that enters your body comes from breathing in lead dust or chemicals that contain lead. Once this lead gets into your lungs, it goes quickly to other parts of the body in your blood.

You may swallow a lot of lead by eating food and drinking liquids that contain it. Most of the lead that enters your body comes through swallowing, even though very little of the amount you swallow actually enters your blood and other parts of your body. The amount that gets into your body from your stomach partially depends on when you ate your last meal. It also depends on how old you are and how well the lead particles you ate dissolved in your stomach juices. Experiments in adult volunteers showed that the amount of lead that got into the body from the stomach was only about 6% in adults who had just eaten. In adults who had not eaten for a day, about 60–80% of the lead from the stomach got into their blood. On the other hand, 50% of the lead swallowed by children enters the blood and other body parts even if their stomachs are full.

Frequent skin contact with lead in the form of lead-containing dusts and soil can result in children swallowing lead through hand-to-mouth behavior. In adults, only a small portion of the lead will pass through your skin and enter your body if it is not washed off after skin contact. More lead can pass through your skin if it is damaged. Certain types of lead compounds, however, may penetrate your skin.

Shortly after lead gets into your body, lead travels in the blood to the "soft tissues," (such as the liver, kidneys, lungs, brain, spleen, muscles, and heart). After several weeks most of the lead then moves into your bones and teeth. In adults, about 94% of the total amount of lead in the body is contained in their bones and teeth. Children, on the other hand, have only about 73% of the lead in their bodies stored in their bones. The rest is in their soft tissues and blood. Part of the lead can stay in your bones for decades. Part of the lead can leave your bones and may reenter your blood and organs at a later time.

Your body does not change lead atoms into any other form. Once it is taken in and distributed to your organs, the lead that is not stored in your bones leaves your body in your urine or your feces. About 99% of the amount of lead that you take into your body will leave in your waste within a couple of weeks, but only about 32% of the lead taken into the body of children will leave in the waste. For more information on how lead can enter and leave your body, please refer to Chapter 2.

1.5 HOW CAN LEAD AFFECT MY HEALTH?

Exposure to lead can be particularly dangerous for unborn children because of their great sensitivity during development. Exposure to lead can also be dangerous for young children because they swallow more lead through normal mouthing activity, take more of the lead that they swallow into their bodies, and are more sensitive to its effects. Unborn children can be exposed to lead through their mothers. This may cause premature births, smaller babies, and decreased mental ability in the infant. Lead exposure may also decrease intelligence quotient (IQ) scores and reduce the growth of young children. These effects have been seen more often following exposure to high levels of lead, than following exposure to low levels of lead.

In adults, lead exposure may decrease reaction time and possibly affect the memory. Lead exposure may also cause weakness in your fingers, wrists, or ankles. Lead exposure may increase blood pressure in middle-aged men. It is not known whether lead has an effect on blood pressure in women. Lead exposure may also cause anemia, a disorder of the blood. The connection between the occurrence of these effects and low lead exposures is not certain. At high levels of exposure, lead can severely damage the brain and kidneys in adults or children. In addition, high levels of exposure to lead may cause abortion and damage the male reproductive system (the organs responsible for sperm production). The effects of lead are the same regardless of whether it enters the body through breathing or swallowing.

Kidney tumors have developed in rats and mice given large doses of lead. We have no proof that lead causes cancer in humans. Furthermore, the animal studies have been criticized by a panel of EPA scientists because of the very high doses used, among other things, and should not be used to predict what may happen in humans. The Department of Health and Human Services has determined that lead acetate and lead phosphate may reasonably be anticipated to be carcinogens based on these studies in animals, but that there is inadequate evidence for the carcinogenicity of these lead compounds in humans. Please see Chapter 2 for more information on the health effects of lead.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO LEAD?

The amount of lead in the blood can be measured to determine if exposure to lead has occurred. This test can give a rough measure of how much lead one has been exposed to. Methods to measure lead in teeth or bones by X-ray techniques, although not widely accessible, also are available. Exposure to lead in the blood can be evaluated by measuring erythrocyte protoporphyrin (EP). EP is a part of red blood cells known to increase when the amount of lead in the blood is high. This method is commonly used to screen children for potential chronic lead poisoning. The Centers for Disease Control and Prevention (CDC) considers children to have an elevated level if the amount of lead in the blood is at least 10 micrograms per deciliter (μg/dL). Medical treatment to lower blood levels has been done if the lead concentrations in blood are higher than 55 μg/dL in children or higher than 70 μg/dL in adults. For more information on tests to measure lead in the body, see Chapters 2 and 6.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The CDC recommends that all children should be screened for lead poisoning at least once a year. This is especially important for children between the ages of 6 months and 6 years. A child with an EP level of 35 μg/dL or greater should be tested for blood lead level. A child with a blood lead level of 20 μg/dL or greater should be tested by their doctors for symptoms of lead poisoning.

EPA requires that the concentration of lead in air that the public breathes shall not exceed 1.5 micrograms per cubic meter ($\mu g/m^3$) averaged over 3 months. EPA regulations now limit the level of lead in leaded gasoline to 0.1 grams per gallon (0.1 g/gal) and the level in unleaded gasoline to 0.05 g/gal. According to the Clean Air Act Amendments (CAAA) of 1990, the sale of leaded gasoline will be illegal as of December 31, 1995.

EPA regulations also limit lead in drinking water to 0.015 milligrams per liter (mg/L). The Consumer Product Safety Commission (CPSC), EPA, and the states are required by the 1988 Lead Contamination Control Act to deal with the problem of lead in drinking water coolers by requiring that water coolers containing lead be recalled or repaired and that new coolers be lead-free. In addition, drinking water in schools must be tested for lead and the sources of lead in this water must be removed.

To help protect small children, the CPSC requires that the concentration of lead in most paints available through normal consumer channels be not more than 0.06%. The CDC recommends that inside and outside painted surfaces of dwellings be tested for lead, and that surfaces containing lead equal to or greater than 0.7 milligram per square centimeter (mg/cm^2) of surface area be stripped and repainted according to a four-step paint removal and replacement protocol. This is necessary because stripping can release fine particles of lead that can cause lead poisoning.

The Department of Housing and Urban Development (HUD) requires that federally funded housing and renovations, public housing, and Indian housing be tested for lead-based paint hazards and that such hazards be fixed by covering the paint or removing it. HUD is carrying out demonstration projects to determine the best ways of covering or removing this paint in housing.

The Occupational Safety and Health Administration (OSHA) regulations limit the concentration of lead in workroom air to 50 $\mu g/m^3$ for an 8-hour workday. If a worker has a blood lead level of 40 $\mu g/dL$, then OSHA requires that worker be removed from the workroom where lead exposure is occurring.

Please see Chapter 7 for more information on federal and state regulations and guidelines for lead.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. These clinics specialize in the recognition, evaluation, and treatment of illnesses resulting from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of lead and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for lead based on toxicological studies and epidemiological investigations.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with the carcinogenic effects of lead are indicated in Figure 2-2.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability and extrapolation of data from laboratory animals to humans.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1989e), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

This chapter will focus primarily on inorganic lead compounds (lead, its salts, and oxides/sulfides), the predominant forms of lead in the environment. The available data on organic (i.e., alkyl) lead compounds indicate that some of the toxicologic effects of alkyl lead appear to be mediated through metabolism to inorganic lead and that during the combustion of gasolines containing alkyl lead significant amounts of inorganic lead are released to contaminate the environment. In addition, the lead alkyl halides in automobile exhausts are quickly oxidized by sunlight and air, and do not appear to be present at hazardous waste sites in significant amounts. By far, most lead at hazardous waste sites is inorganic lead. The limited data available on alkyl lead compounds indicate that the toxicokinetic profiles and toxicological effects of these compounds are qualitatively and quantitatively different from those of inorganic lead (EPA 1985b).

The database for lead is unusual in that it contains a great deal of data concerning dose-effect relationships in humans. These data come primarily from studies of occupationally exposed groups and the general population. However, the dose data for humans are generally expressed in terms of absorbed dose, usually measured as levels of lead in the blood. Dose-effect data in terms of external exposure levels, or milligrams per kilogram per day (mg/kg/day) doses of lead by a single route of exposure are not generally available for humans. Exposure to lead in occupational studies is primarily through inhalation, although some contribution to body burden is derived from the oral route. Conversely, the general population, including children, is exposed to lead primarily through the oral route, but with some contribution to body burden through inhalation. The effects of lead are the same regardless of the route of entry into the body, and they are correlated with internal exposure as blood lead level. For these reasons, this section of the profile will not attempt to separate human dose data by routes of exposure (unless these data are available) but will present it in terms of blood lead levels in Section 2.2.1. Most of the human data therefore cannot be displayed graphically by the methods previously described; these data require a different approach, based on blood lead levels. Nonetheless, human data are the best basis for any assessment of potential health effects from lead exposure to persons living or working near hazardous waste sites or other populations at risk. Experimental studies of lead toxicity in animals provide support for observations in human studies, with some consistency in types of effects and blood-lead-effect relationships. However, animal data on lead toxicity are generally considered less suitable as the basis for health effects assessments than are the human data. There is no absolutely equivalent animal model for the effects of lead on humans.

Data concerning dose-effect relationships in animals are available not only in terms of blood lead levels but also in terms of external exposure levels or mg/kg/day doses. The animal data are presented in Sections 2.2.2, 2.2.3, and 2.2.4 and can be displayed graphically by methods previously described. However, the graphical presentation will be done primarily for consistency with other toxicological profiles in this series and is not recommended for use in assessing possible health hazards to persons living or working near waste sites. MRLs were not derived because no thresholds have been demonstrated for the most sensitive effects in humans.

2.2.1 Effects in Humans Based on Blood Lead Levels

As discussed in the introduction to Section 2.2, the bulk of the human data on the health effects of lead are expressed in terms of internal exposure, or blood lead levels, rather than external exposure levels (i.e., mg/m^3 or mg/kg/day). As stated earlier, for the general population, exposure to lead occurs primarily via the oral route with some contribution from the inhalation route, whereas occupational exposure is primarily by inhalation with some oral. Therefore, it is difficult to distinguish specific routes and levels of exposure. For this reason, the human health effects data for lead will be presented in terms of blood lead levels in this section.

Blood lead concentrations reflect the absorbed dose of lead. However, since lead has a long body half-life because of the major body lead sink being bone, the interpretation of blood lead data depends on a knowledge of the past history of exposure to lead. Thus, in the absence of intense exposure to lead for a considerable period up to its body half-life, the blood lead concentrations reflect recent lead exposures. However, if intermittent exposure to lead is occurring in several distinct environments, the blood lead concentration reflects both recent and past exposures to lead. Thus, biological effects for populations with the same blood lead concentrations may not be the same since different exposure times scales may be involved. This is the reason why free erythrocyte protoporphyrin (FEP) and erythrocyte zinc protoporphyrin (ZPP) have been utilized as additional biological markers since their elevation is more related to chronic lead exposure than acute lead exposure (see Section 2.5).

A major limitation inherent in a good portion of the human health effects studies is that exposure durations, and sometimes blood lead levels, are not specified. However, many of the studies deficient in experiment detail still provide useful information, and they will be discussed in this section even if they are not recorded in Table 2-1.

2.2.1.1 Death

Mortality studies for workers exposed occupationally to lead are available. These studies all report discrepant results, and all are limited with respect to study design. Therefore, no firm conclusions regarding cause and effect can be drawn from these studies relative to a minimum lethal dose. A cohort mortality study of employees at lead-producing facilities was conducted (Cooper 1988; Cooper et al. 1985). Two cohorts of male lead workers, 4,519 battery plant workers and 2,300 lead production workers, all of whom had been employed for at least 1 year during the period 1946–1970, were studied for mortality from 1947 through 1980. Overall mortality and standardized mortality ratios (SMRs) were determined. From 1947 through 1972, mean blood lead levels were determined to be 63 μg/dL for 1,326 battery plant workers and 80 μg/dL for 537 lead production workers. (Blood lead data were not available for many of the workers and most of the monitoring was done after 1960.) The number of observed deaths from all causes combined was significantly greater ($p<0.01$) than expected for both groups based on national mortality rates for white males. The increased mortality rates resulted in large part from malignant neoplasms; chronic renal disease, including hypertension and nephritis; and "ill-defined" causes. A limitation of this study is the lack of control for potentially confounding factors such as exposures to other chemicals, smoking, ethnicity, diet, and alcohol.

Two studies of mortality in four lead acid battery plants in England were conducted (Fanning 1988; Malcolm and Barnett 1982). In the report by Malcolm and Barnett (1982), causes of death between 1925 and 1976 of workers with no, low, or high lead exposure were compared to national mortality rates. In the high lead exposure group, a slight, but not statistically significant, increase in deaths due to cerebrovascular disease was observed. However, among the workers aged 65–69 years, death due to cerebrovascular disease was significantly increased. In addition, a marginally significant increase in the incidence of deaths due to nephritis and nephrosis was observed in the combined low- and high-exposure groups during 1935–1958, but not at later periods. A significant increase in cancer of the digestive tract among the high-exposure group was observed among those workers who died during employment, but not among retirees. The interpretation of this finding relative to lead effects was questioned by the authors. However, it may be that these retirees are the less susceptible members of the population.

TABLE 2-1. Health Effects Associated with Exposure to Lead and Internal Lead Doses in Humans

Duration of exposure	System	Effect	Blood lead levels at which effect observed (µg/dL)	Reference
>1 yr (occup)		Increase in death due to hypertension, nephritis, neoplasms	63–80	Cooper et al. 1985, 1988
NS (occup)		Increase in death due to cerebrovascular disease, nephritis, and/or nephrosis	NS	Fanning 1988; Malcolm and Barnett 1982; Michaels et al. 1991
>3 yr (occup)		No increase in deaths	34–58 (means)	Gerhardsson et al. 1986b
NS		Acute encephalopathy resulting in death in children	125–750	NAS 1972
2 wk->1 yr (occup)	Cardiovascular	Increased blood pressure	≥30–120	deKort et al. 1987; Pollock and Ibels 1986; Marino et al. 1989; Weiss et al. 1986, 1988
>1 yr (occup)	Cardiovascular	No effect on blood pressure	40 (mean)	Parkinson et al. 1987
>1 yr (occup)	Cardiovascular	Ischemic electrocardiogram changes	51 (mean)	Kirkby and Gyntelberg 1985
NS (general population)	Cardiovascular	Increased blood pressure	44.9 (mean)	Khera et al. 1980b
NS (general population)	Cardiovascular	Increased systolic pressure by 1–2 mmHg and increased diastolic pressure by 1.4 mmHg with every doubling in blood lead level; effect most prominent in middle-aged white men	7–38	Coate and Fowles 1989; Harlan 1988; Harlan et al. 1988; Landis and Flegal 1988; Pirkle et al. 1985; Schwartz 1988
NS (general population)	Cardiovascular	No significant correlation between blood pressure and blood lead levels	6–13 (median) or NS	Elwood et al. 1988; Grandjean et al. 1989; Neri et al. 1988; Staessen et al. 1990, 1991
NS (general population)	Cardiovascular	Degenerative changes in myocardium, electrocardiogram abnormalities in children	6–20	Silver and Rodriquez-Torres 1968

TABLE 2-1 (Continued)

Duration of exposure	System	Effect	Blood lead levels at which effect observed (µg/dL)	Reference
NS (acute) (occup)	Gastrointestinal	Colic (abdominal pain, constipation, cramps, nausea, vomiting, anorexia, weight loss)	40-200	Awad et al. 1986; Baker et al. 1979; Haenninen et al. 1979; Holness and Nethercott 1988; Kumar et al. 1987; Marino et al. 1989; Matte et al. 1989; Muijser et al. 1987; Pagliuca et al. 1990; Pollock and Ibels 1986; Schneitzer et al. 1990
NS (acute) (general population)	Gastrointestinal	Colic in children	60-100	EPA 1986a; NAS 1972
NS (occup)	Hematological	Increased ALAS and/or decreased ALAD	87 or NS (correlated with blood lead level)	Alessio et al. 1976; Meredith et al. 1978; Wada et al. 1973
NS (general population)	Hematological	Decreased ALAD	3-56 (adult) No threshold (children)	Chisholm et al. 1985; Hernberg and Nikkanen 1970; Lauwerys et al. 1978; Roels et al. 1976; Roels and Lauwerys 1987; Secchi et al. 1974
NS (occup)	Hematological	Increased urinary or blood ALA	<40-50, 87 (mean) or NS	Lauwerys et al. 1974; Meredith et al. 1978; Pollock and Ibels 1986; Selander and Cramer 1970
NS (general population)	Hematological	Increased urinary ALA	>35 (adult) 25-75 (children)	NAS 1972; Roels and Lauwerys 1987
NS (general population)	Hematological	Increased FEP	≥25-35	Grandjean and Lintrup 1978; Roels et al. 1975
NS (general population)	Hematological	Increased EP	30-40 (males) 20-30 (females)	Roels et al. 1979; Roels and Lauwerys 1987; Roels et al. 1975, 1976, 1979; Stuick 1974
NS (general population)	Hematological	Increased ZPP	≥15 (children)	Hammond et al. 1985; Piomelli et al. 1982; Rabinowitz et al. 1986; Roels and Lauwerys 1987; Roels et al. 1976
NS (general population)	Hematological	Increased urinary coproporphyrin	≥35 (children) ≥40 (adults)	EPA 1986a

TABLE 2-1 (Continued)

Duration of exposure	System	Effect	Blood lead levels at which effect observed (µg/dL)	Reference
NS (occup)	Hematological	Decreased hemoglobin with or without basophilic stippling of erythrocytes	≥40	Awad et al. 1986; Baker et al. 1979; Grandjean 1979; Lilis et al. 1978; Pagliuca et al. 1990; Tola et al. 1973; Wada et al. 1973
NS (general population)	Hematological	Decreased hemoglobin	≥40 (children)	Adebonojo 1974; Betts et al. 1973; Pueschel et al. 1972; Rosen et al. 1974
NS (general population)	Hematological	Anemia (hematocrit of <35%)	>20 (children)	Schwartz et al. 1990
NS (occup)	Hematological	Decreased Py-5'-N	NS	Buc and Kaplan 1978; Paglia et al. 1975, 1977
NS (general population)	Hematological	Decreased Py-5'-N	7–80 (children)	Angle and McIntire 1978; Angle et al. 1982
NS (acute) (general population)	Hepatic	Decreased mixed function oxidase activity	NS (children)	Alvares et al. 1975; Saenger et al. 1984
NS (chronic) (occup)	Renal	Chronic nephropathy	40–>100	Biagini et al. 1977; Cramer et al. 1974; Lilis et al. 1968; Maranelli and Apostoli 1987; Ong et al. 1987; Pollock and Ibels 1986; Verschoor et al. 1987; Wedeen et al. 1979
1-30 yr (occup)	Renal	No effect on renal function	40–61	Buchet et al. 1980; Huang et al. 1988a
NS (chronic) (general population)	Renal	Renal impairment with gout or hypertension	18–26 µg/dL	Batuman et al. 1981, 1983
NS (acute) (general population)	Renal	Aminoaciduria; Fanconi syndrome	>80 (children)	Chisolm 1962; Pueschel et al. 1972
0.1-20 yr (chronic) (occup)	Other	Decreased thyroxin (T_4)	≥56	Tuppurainen et al. 1988

TABLE 2-1 (Continued)

Duration of exposure	System	Effect	Blood lead levels at which effect observed (µg/dL)	Reference
NS (chronic) (general population)	Other	No effect on thyroid function in children	2–77 (levels measured)	Siegel et al. 1989
NS (general population)	Other	Negative correlation between blood lead and serum 1,25-dihydroxyvitamin D in children	12–120	Mahaffey et al. 1982; Rosen et al. 1980
NS (chronic) (general population)	Other	No effect on vitamin D metabolism in children	5–24 (levels measured)	Koo et al. 1991
NS (chronic) (general population)	Other	Growth retardation in children	≥30–60; Tooth lead >18.7 µg/g	Angle and Kuntzelman 1989; Lauwers et al. 1986; Lyngbye et al. 1987
NS (chronic) (general population)	Other	No association between blood lead levels and growth in children	10–47 (levels measured)	Greene and Ernhart 1991; Sachs and Moel 1989
<18 yr (occup)	Immunological	Depression of cellular immune function, but no effect on humoral immune function	21–90	Alomran and Shleamoon 1988; Ewers et al. 1982
NS (acute)	Neurological	Encephalopathy (adults)	50–>300	Kehoe 1961a; Kumar et al. 1987; Smith et al. 1938
NS (acute and chronic) (occup)	Neurological	Neurological signs and symptoms in adults including malaise, forgetfulness, irritability, lethargy, headache, fatigue, impotence, decreased libido, dizziness, weakness, paresthesia	40–80	Awad et al. 1986; Baker et al.1979; Campara et al. 1984; Haenninen et al. 1979; Holness and Nethercott 1988; Marino et al. 1989; Matte et al. 1989; Pagliuca et al. 1990; Parkinson et al. 1986; Pasternak et al. 1989; Pollock and Ibels 1986; Schneitzer et al. 1990; Zimmerman-Tansella et al. 1983

TABLE 2-1 (Continued)

Duration of exposure	System	Effect	Blood lead levels at which effect observed (µg/dL)	Reference
NS (occup)	Neurological	Neurobehavioral function in adults; disturbances in oculomotor function, reaction time, visual motor performance, hand dexterity, IQ test and cognitive performance, nervousness, mood, coping ability, memory	40–80	Arnvig et al. 1980; Baker et al. 1983; Baloh et al. 1979; Campara et al. 1984; Glickman et al. 1984; Haenninen et al. 1978; Hogstedt et al. 1983; Mantere et al. 1982; Spivey et al. 1980; Stollery et al. 1989; Valciukas et al. 1978; Williamson and Teo 1986
NS (occup)	Neurological	No effect on neurobehavioral function in adults	40–60 (levels measured)	Milburn et al. 1976; Ryan et al. 1987
NS (occup)	Neurological	Peripheral nerve function in adults; decreased nerve conduction velocity	30–≥70	Araki et al. 1980; Muijser et al. 1987; Rosen et al. 1983; Seppalainen et al. 1983; Triebig et al. 1984
NS (occup)	Neurological	No effect on peripheral nerve function	60–80 (levels measured)	Spivey et al. 1980
NS (general population)	Neurological	Neurological signs and symptoms in children and encephalopathy	60–450 (effects other than encephalopathy); >80–800 (encephalopathy)	Bradley and Baumgartner 1958; Bradley et al. 1956; Chisolm 1962, 1965; Chisolm and Harrison 1956; Gant 1938; Rummo et al. 1979; Smith et al. 1983
NS (general population)	Neurological	Neurobehavioral function in children: lower IQs and other neuropsychologic deficits	40–200	dela Burde and Choate 1972, 1975; Ernhart et al. 1981; Kotok 1972; Kotok et al. 1977; Rummo et al. 1979
NS (general population)	Neurological	Neurobehavioral function in children: slightly decreased performance on IQ tests and other measures of neuropsychological function	Tooth lead: 6–>30 µg/g Blood lead: 6–60	Bellinger and Needleman 1983; Bergomi et al. 1989; Fulton et al. 1987; Hansen et al. 1989; Hawk et al. 1986; Needleman et al. 1979; Needleman et al. 1985; Needleman et al. 1990; Schroeder et al. 1985; Schroeder and Hawk 1987; Silva et al. 1988; Wang et al. 1989

TABLE 2-1 (Continued)

Duration of exposure	System	Effect	Blood lead levels at which effect observed (µg/dL)	Reference
NS (general population)	Neurological	No correlation between blood lead levels and permanent effects on neurobehavioral development in children	10–15	Cooney et al. 1989a; Harvey et al. 1984, 1988; Lansdown et al. 1986; McBride et al. 1982; Ernhart et al. 1990; Dietrich et al. 1987a; Bellinger et al. 1989a; McMichael et al. 1986; Pocock et al. 1989; Smith et al. 1983; Winneke et al. 1984
NS (general population)	Neurological	Decrease in hearing acuity in children	4–60	Robinson et al. 1985; Schwartz and Otto 1987
NS (general population)	Neurological	Alterations in peripheral nerve function in children	20–30	Erenberg et al. 1974; Landrigan et al. 1976; Schwartz et al. 1988; Seto and Freeman 1964
prenatal (general population)	Developmental	Decreased growth rate	7.7	Shukla et al. 1989
prenatal (general population)	Developmental	Reduced birth weight and/or reduced gestational age, and/or increased incidence of still-birth and neonatal death	12–17	Bornschein et al. 1989; McMichael et al. 1986; Moore et al. 1982; Ward et al. 1987; Wibberley et al. 1977
NS (general population)	Developmental	No association between blood lead levels and birth weight, gestational age, or other neonatal size measures	3–55	Greene and Ernhart 1991; Factor-Litvak et al. 1991
NS (general population)	Developmental	Impaired mental development in children	10–15	Baghurst et al. 1987; Bellinger et al. 1984, 1985a, 1985b, 1986a, 1986b, 1987a, 1987b; Bornschein et al. 1989; Dietrich et al. 1986, 1987a, 1987b; Ernhart et al. 1985, 1986, 1987; McMichael et al. 1988; Rothenberg et al. 1989a; Wigg et al. 1988; Winneke et al. 1985a, 1985b; Wolf et al. 1985; Vimpani et al. 1985, 1989
NS (general population)	Developmental	Inverse correlation between blood lead levels and ALA and ALAD activity	10–33 (mean)	Haas et al. 1972; Kuhnert et al. 1977; Lauwerys et al. 1978

TABLE 2-1 (Continued)

Duration of exposure	System	Effect	Blood lead levels at which effect observed (µg/dL)	Reference
NS (general population)	Reproductive	Increased incidence of miscarriages and stillbirths in exposed women	≥10 or NS	Baghurst et al. 1987; Hu et al. 1991; McMichael et al. 1986; Nordstrom et al. 1979; Wibberley et al. 1977
NS (general population)	Reproductive	No association between blood lead levels and the incidence of spontaneous abortion in exposed women	2	Murphy et al. 1990
NS (occup)	Reproductive	Adverse effects on testes	40-50	Assennato et al. 1987; Braunstein et al. 1978; Chowdhury et al. 1986; Cullen et al. 1984; Lancranjan et al. 1975; Rodamilans et al. 1988; Wildt et al. 1983

ALA = δ-aminolevulinic acid; ALAD = δ-aminolevulinic acid dehydratase; ALAS = δ-aminolevulinic acid synthase; EP = erythrocyte protoporphyrins; FEP = free erythrocyte protoporphyrins; IQ = intelligence quotient; mmHg = millimeters of mercury; NS = not specified; (occup) = occupational; Py-5'-N = pyrimidine-5-nucleotidase; wk = week(s); yr = year(s); ZPP = erythrocyte protoporphyrin

In the second study (Fanning 1988), a case-control study was conducted to compare the causes of death among 867 workers exposed to lead from 1926 to 1985 with 1,206 workers having low or no lead exposure. Environmental lead levels and biological monitoring for body lead burdens were not available for the entire period. A significant increase in deaths due to cerebrovascular disease was found in lead workers that died between 1946 and 1965 as compared to controls. No other cause produced an excess of deaths in lead workers. The author suggested that the increased risk of death due to cerebrovascular disease was not present from 1965 to 1985 because of stricter occupational standards resulting in lower levels of exposure. Because environmental lead levels and/or lead body burdens were not quantified for the entire period of study, the possibility of misclassification of workers exists. Furthermore, it does not appear that various confounding factors, such as age, smoking, etc., were accounted for in this study.

Increased risk of death due to cerebrovascular disease was also observed in a cohort of 1,261 white male newspaper printers (typesetters) (Michaels et al. 1991). The cohort was followed from January 1961 through December 1984. While neither environmental levels of lead nor blood lead levels were measured, it was assumed by the study authors that exposure was generally below the OSHA Permissible Exposure Limit (PEL) of 50 $\mu g/m^3$ based on historical industrial hygiene studies in the printing industry. Furthermore, these workers had little or no occupational exposure to any other potentially toxic agents. Information on death and length of employment (used as a surrogate for duration of exposure) was obtained from union records. It was assumed that lead exposure ceased in 1976 when the transition to computerized typesetting occurred. SMRs were calculated for 92 cause-of-death categories using the mortality rates of New York City as the comparison population. The authors found that there were no significantly elevated nonmalignant or malignant causes of death in this cohort. In fact, the SMRs were generally less than unity, indicating that there were less deaths than expected, which the authors attributed to the "healthy worker effect." However, the SMR for cerebrovascular disease was significantly elevated in those members of the cohort employed for more than 30 years. This was not accompanied by an excess of arteriosclerotic heart disease, which suggests that lead exposure selectively increases the effect of cerebrovascular disease. This study is limited in that actual exposure levels and/or blood lead levels were not measured.

In another cohort mortality study that compared the mortality rates due to various causes in 437 Swedish smelter workers exposed to lead for at least 3 years from 1950 to 1974, the results indicated that there was no statistically significant increase in mortality associated with lead exposure (Gerhardsson et al. 1986b). The mortality data for these workers were compared with national and county mortality rates specified for cause, sex, and calendar periods. Environmental lead levels and blood lead levels were available for all workers since 1950. Mean blood lead was 58 $\mu g/dL$ in 1950 and 34 $\mu g/dL$ in 1974. The group of 437 lead-exposed workers was further subdivided into high and low mean blood lead levels and high and low peak blood levels. No statistically significant increases in mortality from any specific cause was found in the lead workers or among the subgroups of lead workers. In addition, no consistent dose-response patterns were seen in the subgroups. Limitations of this study include the fact that it did not account for various confounding factors, such as smoking and all of the workers were exposed to other toxic chemicals, such as antimony, arsenic, cadmium, chromium, cobalt, lanthanum, selenium, zinc, benzo(a)pyrene, and short-lived free radicals.

In summary, while no strong conclusions can be drawn based on these mortality studies, it is important to note that three of these studies (Fanning 1988; Malcolm and Barnett 1982; Michaels et al. 1991) reported some elevation, whether statistically significant or not, in deaths due to cerebrovascular disease. Here, the replication across studies that differed in strengths and deficiencies is perhaps more telling than the strength of the conclusion drawn from any one of these studies.

High levels of lead have been suggested as a causative agent in Sudden Infant Death Syndrome (SIDS) (Drasch et al. 1988). Blood lead levels in 41 victims of SIDS (3.9±1.8 μg/dL) were compared to those of 77 living control babies (3.5±1.2 μg/dL) and 5 babies of the same ages who died from traumatic causes (3.5±2.1 μg/dL). The authors controlled for several factors that may influence blood lead levels, including post-mortem shifts in blood water, age, sex, social class, nutrition, fever prior to death or sampling, birth weight, complications at birth, premature birth, and pregnancy history of the mothers. None of these factors differed significantly between the SIDS babies and the control babies. The post-mortem shift in blood water was accounted for by calculation of the lead concentration in blood dry weight. There was no significant difference between either the arithmetic or geometric means of the dry blood lead concentration for the SIDS and control babies. However, a significantly greater number of the highest lead concentrations in dry blood were found in the SIDS group than in the control babies ($p<0.01$) as determined by chi-square analysis. Based on these results, there may be an association between higher body burdens of lead and SIDS, but the mechanism behind this association cannot be determined at this time. Possibilities include an effect of lead on prenatal and/or postnatal neurological development.

In children, entry of lead into the body occurs primarily by ingestion, although inhalation also contributes to body burden. Once lead intoxication has proceeded to encephalopathy, the risk of death exists. Dose-response information on a pediatric population relating blood lead levels with the occurrence of acute encephalopathy and death was compiled by the National Academy of Sciences (NAS 1972) using unpublished data from groups of patients originally reported by Chisolm (1962) and Chisolm and Harrison (1956). The range of blood levels associated with encephalopathy was approximately 90–800 μg/dL (mean ≈330 μg/dL), and the range associated with death was approximately 125–750 μg/dL (mean = 327 μg/dL). All but 1 of the 98 cases of fatal encephalopathy had blood levels ≥150 μg/dL.

2.2.1.2 Systemic Effects

No studies were located regarding musculoskeletal or dermal/ocular effects in humans after exposure to lead.

Respiratory Effects. The only information located regarding respiratory effects in humans associated with lead exposure was a case report of a 41-year-old man who was exposed to lead for 6 years while removing old lead-based paint from a bridge. At the time of the initial assessment, his blood lead level was 87 μg/dL, and he complained of mild dyspnea for the last 2-3 years. No abnormalities in respiratory function were seen at clinical examination, so it is not possible to conclude that his respiratory symptoms were related to exposure to lead (Pollock and Ibels 1986).

Cardiovascular Effects. There is currently considerable scientific debate as to whether there is a causal relationship between lead exposure and hypertension. Another area of controversy is whether African Americans are more susceptible to the effects of lead than are Caucasians or Hispanics. The evidence from both occupational studies and large-scale general population studies (i.e., National Health and Nutrition Examination Survey [NHANES II], British Regional Heart Study [BRHS]) is not sufficient to conclude that such a causal relationship exists between blood lead levels and increases in blood pressure. The database on lead-induced effects on cardiovascular function in humans will be discussed by presenting a summary of several representative occupational studies followed by a discussion of the findings from the large-scale general population studies.

Cardiovascular effects have been noted in occupationally exposed workers after exposure to high levels of lead following exposure durations of as short as 4 weeks. Construction workers (race not specified) using oxyacetylene torches to cut a metal bridge that had been painted with lead-based paint were reported to exhibit increases in heart rate and blood pressure after 4 weeks of exposure (Marino et al. 1989). Steep increases in blood lead levels were observed only 2 weeks after work began. Peak blood lead levels ranged from 48 to 120 μg/dL. Personal breathing zone exposure to airborne lead ranged from 600 to 4,000 $\mu g/m^3$. Hypertension was also observed in another group of men (race not specified) who removed lead-based paint from a metal bridge for varying lengths of time (Pollock and Ibels 1986). Blood lead levels measured in these workers ranged from 50 to 85 μg/dL; two of the five cases also exhibited nephropathy and one complained of angina.

Another occupational study compared 53 lead-exposed male workers (2 noncaucasian, 51 caucasian) (mean blood lead = 47.4 μg/dL, range = ≤60–70 μg/dL) from a plant processing lead and cadmium compounds with a control group of 52 workers (8 noncaucasian, 44 caucasian) (mean blood lead = 8.1 μg/dL, with none exceeding 20 μg/dL) from a nonlead industry (de Kort et al. 1987). Blood pressure levels were positively correlated with blood lead and urine cadmium levels, but not with blood cadmium levels. The correlation for systolic blood pressure and blood lead level remained significant after controlling for confounding variables.

The relationship of blood lead level to systolic and diastolic blood pressure was determined in a study of 89 Boston policemen (race not specified) (Weiss et al. 1986, 1988). These policemen were under observation for health outcomes related to environmental work exposures (i.e., they had traffic exposure histories). After statistically adjusting for previous systolic blood pressure, body mass index, age, and cigarette smoking, high blood lead level (≥30 μg/dL) was a significant ($p=0.01$) predictor of subsequent elevation in systolic blood pressure of 1.5–11 mmHg in the working policemen with normal blood pressure. Low blood lead level (20–29 μg/dL) was not a predictor of subsequent systolic blood pressure elevations. Diastolic pressure was unrelated to blood lead levels.

Each of the four studies discussed above (de Kort et al. 1987; Marino et al. 1989; Pollock and Ibels 1986; Weiss et al. 1986, 1988) involved cohorts of fewer than 100 subjects and failed to control for one or more significant confounding factors, such as smoking and alcohol intake. Therefore, the conclusions that can be drawn from these studies are of limited usefulness.

On the other hand, another occupational study failed to reveal any significant correlation between occupational lead exposure and diastolic and systolic blood pressure (Parkinson et al. 1987). After controlling for known risk factors (e.g., age, education, income, cigarette usage, alcohol consumption, and exercise), the association between exposure and blood pressure was found to be small and nonsignificant when a group of randomly selected white battery plant workers ($n=270$) was compared to 158 nonexposed workers. The average blood lead of exposed workers was 40±13 μg/dL; in nonexposed workers it was 7±5 μg/dL.

One cohort mortality study (Fanning 1988) has reported an increased mortality rate due to circulatory disease, whereas two others found no such correlation (Cooper 1988; Gerhardsson et al. 1986b) as discussed in Section 2.2.1.1 (Table 2-1). An increased risk of death due to cerebrovascular disease was observed in a cohort of 1,261 white male newspaper printers (typesetters) (Michaels et al. 1991) (see Section 2.2.1.1).

Cardiovascular effects other than blood pressure changes have also been observed in individuals occupationally exposed to lead. For example, 66% of a group of adults ≥46 years old with chronic lead poisoning of occupational origin had electrocardiographic (ECG) abnormalities, a rate four times the adjusted normal rate for that age group (Kosmider and Petelenz 1962). A study of 95 lead smelter workers (mean blood lead = 51 μg/dL) and matched unexposed controls (mean blood lead = 11 μg/dL) revealed a significantly higher incidence of ischemic ECG changes (20%) in the lead workers than in controls (6%) (Kirkby and Gyntelberg 1985). In addition, a slight (4–5 mmHg) but significant increase in diastolic blood pressure was seen in the lead workers relative to controls. Systolic blood pressure was not affected.

Hypertension has also been associated with lead exposure in the general population. In a case-control study of clinically defined groups, 38 male cardiovascular patients were compared with 48 matched normotensive patients (Khera et al. 1980b). The cardiovascular patients were found to have higher blood lead levels (mean = 44.9 μg/dL) than the normotensive patients (mean = 29.0 μg/dL). However, this study is limited by small sample size and incomplete control of confounding factors.

Two large-scale general population studies, the BHRS (Pocock et al. 1984, 1985, 1988) and NHANES II (Coate and Fowles 1989; Gartside 1988; Harlan 1988; Harlan et al. 1988; Landis and Flegal 1988; Pirkle et al. 1985; Schwartz 1988), examined the relationship between blood lead levels and blood pressure in men. Relationships between blood lead levels and hypertension were evaluated in a clinical survey of 7,735 men, aged 40–49 years, from 24 British towns in the BHRS (Pocock et al. 1984, 1985, 1988). A small but significant correlation between systolic blood pressure and blood lead level was found. Of the 74 men with blood lead levels higher than 37 μg/dL, a higher proportion had systolic or diastolic hypertension than did all other men combined. Reanalysis of the same data resulted in highly significant associations between both systolic and diastolic blood pressure and blood lead levels when adjustments were made for variation due to site (town) in multiple regression analyses (Pocock et al. 1985). However, when these data were reanalyzed again, it was concluded that the relationship, although statistically significant, was extremely weak and of dubious biological significance (Pocock et al. 1988). In the 1988 reanalysis (using multiple regression analysis), confounding factors, such as town of residence, alcohol consumption, body mass index, age, cigarette smoking, and social class were adjusted for, and it was found that a number of these factors (e.g., alcohol consumption) had a greater influence on blood pressure than did blood lead level. This reanalysis found that mean systolic blood pressure increased by 1.45 mmHg and diastolic blood pressure increased by 1.25 mmHg for every doubling in blood lead level, with the correlation coefficients attaining statistical significance only because of the very large number of subjects in the survey. Indeed, when separate univariate regression analyses were conducted on each town (i.e., smaller sample size), there was no consistency among the regression coefficients obtained, indicating the high random variability and the weakness of the association. In addition, when the blood lead levels of 316 men who experienced cardiovascular events associated with major ischemic heart disease were compared to those of the rest of the cohort and adjustment was made for age, number of years smoking cigarettes, and town of residence, the excess in blood lead level among the ischemic heart diseases cases was 0.014 μmole/L (0.03 μg/dL), which is not a statistically significant difference. Based on their reanalyses, these authors concluded that ". . . we see no convincing epidemiological evidence at present to support the claim that moderate elevations in body lead burden are of relevance to the risk of cardiovascular disease" (Pocock et al. 1988).

Simple correlational analysis of the NHANES II data by Harlan (1988) and Harlan et al. (1988) revealed statistically significant associations between blood lead levels and systolic and diastolic blood pressure for both men and women, aged 12–74 years. Statistical analyses controlling for a number of other potentially confounding factors (e.g., age, race, and body mass index), however, indicated significant associations between blood lead level and blood pressure only for the men. Based on these analyses, the effect of blood lead concentration on blood pressure was estimated to be an increase in blood pressure of 7 mmHg at blood lead levels between 14 and 30 μg/dL.

Additional analyses of the same data set by Pirkle et al. (1985) focused on white males (40–59 years of age) in order to avoid the effects of colinearity between blood lead levels and blood pressure evident at younger ages and because of a less extensive database for nonwhites. Statistical analyses again revealed significant correlations between blood lead level and blood pressure. No threshold was found below which blood lead level was not significantly related to systolic or diastolic blood pressure across a range of 7–38 μg/dL. Moreover, the analysis by Pirkle et al. (1985) showed that large initial increments in blood pressure occurred at relatively low blood lead levels, with a diminution of blood pressure increments at higher blood lead levels. Lead was a significant predictor of diastolic blood pressure of ≥90 mmHg, the criterion now employed in the United States to define hypertension.

Other analyses of the NHANES II data for men have addressed the issue of possible time-trend effects confounded by variations in sampling sites (Landis and Flegal 1988; Schwartz 1988). These analyses confirm that correlations between systolic or diastolic blood pressure and blood lead levels in men remain significant when site is included as a variable in multiple regression analyses. However, Schwartz (1988) extrapolated these data from males aged 40–59 years to all males aged 20–74 years, which is a questionable statistical practice. In a separate analysis of the NHANES II data, Gartside (1988) examined the relationship between blood lead and systolic and diastolic blood pressure for 26 different age groups, and concluded that there was no convincing evidence of an association between blood lead and blood pressure as reported by Schwartz (1988). Forward stepwise regression analyses were conducted on 64 data sets corresponding to separate communities for white males, white females, and blacks by incremental age groups. Other variables such as demographic, socioeconomic, and dietary factors were fit into the analyses. Forward stepwise regression analysis has the advantage of not overinflating the error rate of any variable, and maximizes the number of respondents included in the analysis. Statistically significantly correlation coefficients were found in only 24 of the 156 analyses (15%). Systolic blood pressure increased about 1.1–4.4 mmHg for every doubling of blood lead in white males, and the largest values were obtained in the older age groups. However, none of these achieved statistical significance. Changes in systolic blood pressure ranged from a loss of 0.9 mmHg to a gain of 0.7 mmHg for every doubling of blood lead in white females; none of these changes were statistically significant. Systolic blood pressure changes ranged from a loss of 4.7 mmHg in the older blacks to a gain of 5.7 mmHg in the younger blacks. Only the changes in the younger age groups achieved statistical significance. All age groups, sexes, and races grouped together resulted in an overall average increase of 1.1 mmHg in systolic blood pressure and 1.4 mmHg in diastolic blood pressure for every doubling of blood lead level. Based on this reanalysis, it can be concluded that the NHANES II data provide a negligible or weak association between blood lead level and blood pressure.

Problems with the NHANES II data cast some doubt on its usefulness for analyzing the relationship between blood lead levels and blood pressure. Data collected in this study on alcohol consumption were not sufficiently detailed for meaningful analysis. In addition, the NHANES II data cover a 4-year period during which there were significant declines in blood lead levels. The National Center for Health Statistics (1986) reported problems with the blood pressure data collected in the NHANES II study. When the NHANES II data were reanalyzed, correcting for the questionable blood pressure data, it was found that the significance and magnitude of the blood lead-blood pressure relationship reported by previous studies (Harlan 1988; Harlan et al. 1988; Landis and Flegal 1988; Pirkle et al. 1985; Schwartz 1988) were far less than reported (Coate and Fowles 1989).

Several other general population studies failed to detect a convincing association between blood lead levels and blood pressure. Two studies were conducted in Wales (the Caerphilly Collaborative Heart Disease Studies and the Welsh Heart Programme) in which blood lead levels and blood pressure were measured in two cohorts of 1,164 men and 868 men and 856 women, respectively (Elwood et al. 1988). The geometric mean blood lead level was 12.7 μg/dL in the first cohort and 11.6 (males) and 9.0 μg/dL (females) in the second cohort. Linear regression analysis, adjusting for age only, revealed no statistically significant relationship between blood lead level and blood pressure. The authors suggest that even if the correlation coefficients were significant, the effect of blood lead on blood pressure would be small. At most a mean rise in both systolic and diastolic pressures of approximately 0.7 mmHg for every 10-μg/dL difference in blood lead was predicted for this population.

A similar study was undertaken in Denmark in a cohort consisting of 451 men and 410 women (Grandjean et al. 1989). A weak but statistically significant association was seen, particularly in the men, between blood lead and systolic and diastolic blood pressures. However, when multiple regression analysis was conducted, adjusting for exercise, smoking, alcohol intake, occupation, height-adjusted weight index, blood hemoglobin, serum cholesterol, and serum triglycerides, no statistically significant association between blood lead level and blood pressure was seen in this cohort. Hemoglobin concentration and alcohol intake correlated best with both blood lead levels and blood pressure; when one or both of these confounders were included in the regression analysis, any statistically significant relationship between blood pressure and blood lead levels was lost for this population.

A negative correlation was found between blood lead and systolic pressure in Belgian men (Staessen et al. 1991). In this study, blood pressure and urinary cation (positive ions found in the urine, such as sodium, potassium, and calcium) concentration data were obtained from 963 men and 1,019 women, and multiple stepwise regression analyses were conducted adjusting for age, body mass index, pulse rate, γ-glutamyltranspeptidase, smoking habits, and use of a contraceptive pill). The only statistically significant association found between blood lead and blood pressure was negative, leading the authors to conclude that there is no biologically significant correlation between blood lead levels and blood pressure for this population.

A study of 398 male and 133 London female civil servants, in which blood pressure, blood lead, and serum creatinine concentrations were measured, found that the positive correlation between blood pressure and blood lead disappeared after adjustment for significant covariates, including gender, age, cigarette smoking, alcohol intake, and body mass index in a stepwise multiple regression analysis (Staessen et al. 1990). The authors concluded that these results do not support "a biologically important relation after adjustment for alcohol intake and other blood pressure covariates" for this type of population.

Both cross-sectional and longitudinal data collected in Canada indicated that there might be a slight association between blood lead and blood pressure (Neri et al. 1988). Analysis of the data from the cross-sectional sampling of the general population (2,193 people, aged 25–64 years) resulted in a zero-order correlation between diastolic blood pressure and a blood lead level of 0.115 that was statistically significant at the $p<0.001$ level. These results can be translated into a blood lead level in excess of the median value of 10 μg/dL being associated with a 37% higher risk of having a diastolic pressure above 90 mmHg. The authors pointed out that the variability in the blood pressure data that was estimated to be at most 3.0 mmHg (0.064 mmHg per unit of blood lead) exceeded any difference in blood pressure that could be attributed to blood lead. Using these same data, multiple regression analyses were conducted including age, body weight/height index, serum zinc, and hemoglobin as possible confounders, and there was no longer a statistically significant relationship between blood lead and blood pressure. These same authors also conducted a longitudinal study of an occupationally exposed group of foundry workers in an attempt to eliminate the high variability in blood pressure seen in the general Canadian population data and to compare blood pressure and blood lead level rises and falls within individuals. Multiple regression analyses, accounting for age and body weight, detected a weak association between blood lead and blood pressure; diastolic and systolic blood pressure increased by 0.298 mmHg and 0.210 mmHg, respectively, for every μg/dL increase in blood lead. However, since the foundry workers were also exposed to cadmium, analysis of the association of cadmium and blood pressure was conducted, and it was found that urinary cadmium levels also correlated with blood lead levels. Therefore, the association observed may not be entirely due to lead.

Taken together, the results of both the occupational and general population studies do not provide conclusive evidence that lead exposure is positively associated with hypertension. The evidence is most convincing in adult men aged 40–59 years old and for systolic rather than diastolic pressure. This association is most apparent for blood lead levels as low as 7 μg/dL for middle-aged men, and a mean increase in systolic blood pressure of 1.0–2.0 mmHg appears to occur for every doubling in blood lead levels in middle-aged men with the increase being somewhat less in adult women. However, when the existing data are adjusted for important confounding factors (e.g., age, body weight index, alcohol consumption, cigarette smoking), the results do not allow for the establishment of a cause-and-effect relationship between blood lead levels and hypertension.

Qualitative evidence linking lead exposure to cardiac effects includes the finding of degenerative changes in cardiac muscle, reported as the proximate cause of death in five fatal cases of lead poisoning in young children with histories of pica (Kline 1960). Additional evidence indicates that ECG abnormalities are fairly common in cases of childhood lead encephalopathy but disappear following chelation therapy (EPA 1986a). For example, abnormal electrocardiograms occurred in 21 of 30 overtly lead-intoxicated children prior to chelation therapy, but in only 4 of these children after therapy (Silver and Rodriguez-Torres 1968).

In adults, a study of 75 autopsies of persons who had resided in a soft-water, leached soil region of North Carolina found a positive correlation between lead level in the aorta and death from heart-related disease (Voors et al. 1982). The association persisted after adjustment for the effect of age. A similar correlation was found between cadmium levels in the liver and death from heart-related disease. (Aortic lead and liver cadmium levels were considered to be suitable indices of exposure.) The effects of the two metals appeared to be additive. Potential confounding variables other than age were not included in the analysis. The investigators stated that fatty liver (indicative of moonshine alcohol consumption) and cigarette smoking did not account for the correlations between lead, cadmium and heart-disease death.

Gastrointestinal Effects. Colic is a consistent early symptom of lead poisoning in occupationally exposed cases or in individuals acutely exposed to high levels of lead, such as occurs during the removal of lead-based paint. Colic is characterized by a combination of the following symptoms: abdominal pain, constipation, cramps, nausea, vomiting, anorexia, and weight loss. Although gastrointestinal symptoms typically occur at blood lead levels of 100–200 μg/dL, they have sometimes been noted in workers whose blood lead levels were as low as 40–60 μg/dL (Awad et al. 1986; Baker et al. 1979; Haenninen et al. 1979; Holness and Nethercott 1988; Kumar et al. 1987; Marino et al. 1989; Matte et al. 1989; Muijser et al. 1987; Pagliuca et al. 1990; Pollock and Ibels 1986; Schneitzer et al. 1990).

Colic is also a symptom of lead poisoning in children. EPA (1986a) has identified a LOAEL of approximately 60–100 μg/dL for children. This value apparently is based on a National Academy of Sciences (NAS 1972) compilation of unpublished data from the patient groups originally discussed in Chisolm (1962, 1965) and Chisolm and Harrison (1956) in which other signs of acute lead poisoning, such as severe constipation, anorexia, and intermittent vomiting, occurred at ≥60 μg/dL.

Hematological Effects. Lead has long been known to have profound effects on heme biosynthesis. In summary, lead inhibits the activity of certain enzymes involved in heme biosynthesis, namely, δ-aminolevulinic acid dehydratase (ALAD), ferrochelatase, and coproporphyrinogen oxidase. As a consequence of these changes, heme biosynthesis is decreased and the activity of the rate limiting enzyme of the pathway, δ-aminolevulinic acid synthetase (ALAS), which is feedback inhibited by heme, is subsequently increased. The end results of these changes in enzyme activities are increased urinary porphyrins, coproporphyrin, and δ-aminolevulinic acid (ALA); increased blood and plasma ALA; and increased erythrocyte protoporphyrin (EP); FEP; and ZPP (EPA 1986a). However, the adverse effects of decreased ALAD and pyrimidine-5'-nucleotidase activities seen at low blood lead levels in the absence of detectable effects on hemoglobin levels and erythrocyte function or survival are not known.

Increases in ALAS activity have been observed in lead workers (Meredith et al. 1978). Leukocyte ALAS was stimulated at a blood lead level of 87 μg/dL (Meredith et al. 1978), a level at which ALAD activity is already significantly inhibited. ALAD activity correlated inversely with blood lead levels in occupationally exposed individuals (Alessio et al. 1976; Wada et al. 1973), as has been seen in subjects with no occupational exposure (Secchi et al. 1974). Erythrocyte ALAD and hepatic ALAD activities were correlated directly with each other and correlated inversely with blood lead levels in the range of 12-56 μg/dL (Secchi et al. 1974).

General population studies indicate that the activity of ALAD is inhibited at very low blood lead levels, with no threshold yet apparent. ALAD activity was inversely correlated with blood lead levels over the entire range of 3-34 μg/dL in urban subjects never exposed occupationally (Hernberg and Nikkanen 1970). Other reports have confirmed the correlation and apparent lack of threshold in different age groups and exposure categories (children--Chisolm et al. 1985; children--Roels and Lauwerys 1987; adults--Roels et al. 1976). Inverse correlations between blood lead levels and ALAD activity were found in mothers (at delivery) and their newborns (cord blood). Blood lead levels ranged from approximately 3 to 30 μg/dL (Lauwerys et al. 1978).

Inhibition of ALAD and stimulation of ALAS result in increased levels of ALA in blood or plasma and in urine. For example, in a case report of a 53-year-old man with an 11-year exposure to lead from removing old lead-based paint from a bridge, a blood lead level of 55 μg/dL was associated with elevated urinary ALA (Pollock and Ibels 1986). The results of the Meredith et al. (1978) study on lead workers and controls indicated an exponential relationship between blood lead and blood ALA. Numerous studies reported direct correlations between blood lead level and log urinary ALA in workers. Some of these studies indicated that correlations can be seen at blood lead levels of <40 μg/dL (Lauwerys et al. 1974; Selander and Cramer 1970), although the slope may be different (less steep) than at blood lead levels of >40 μg/dL.

Correlations between blood lead levels and urinary ALA similar to those observed in occupationally exposed adults have also been reported in non-occupationally exposed adults (Roels and Lauwerys 1987) and children (unpublished data of J.J. Chisolm, Jr., reported by NAS 1972). Linear regression analyses conducted on data obtained from 39 men and 36 women revealed that increases in urinary ALA may occur at blood lead levels of >35 μg/dL in women and >45 μg/dL in men (Roels and Lauwerys 1987). A significant linear correlation between blood lead level and log ALA was obtained for data in children 1-5 years old with blood lead levels of 25-75 μg/dL. The correlation was seen primarily at blood lead levels >40 μg/dL, but some correlation may persist at <40 μg/dL (NAS 1972).

A dose-related elevation of EP or ZPP in lead workers has been documented extensively (Herber 1980; Matte et al. 1989). Correlations between blood lead levels and log EP or ZPP indicate an apparent threshold for EP elevation in male workers at 25–35 μg/dL (Grandjean and Lintrup 1978; Roels et al. 1975) for FEP and a threshold of 30–40 μg/dL for EP (Roels and Lauwerys 1987; Roels et al. 1979). The threshold for EP elevation appears to be somewhat lower (20–30 μg/dL) in women than in men (Roels and Lauwerys 1987; Roels et al. 1975, 1976, 1979; Stuik 1974), regardless of whether exposure is primarily by inhalation (occupational) or oral (nonoccupational). These studies were controlled for possible confounding factors such as iron deficiency or age, both of which increase erythrocyte ZPP.

Many studies have reported the elevation of EP or ZPP as being exponentially correlated with blood lead levels in children. However, peak ZPP levels lag behind peak levels of blood lead. The threshold for this effect in children is approximately 15 μg/dL (Hammond et al. 1985; Piomelli et al. 1982; Rabinowitz et al. 1986; Roels and Lauwerys 1987; Roels et al. 1976), and may be lower in the presence of iron deficiency (Mahaffey and Annest 1986; Marcus and Schwartz 1987). A recently published study suggests that the current CDC standard for acceptable blood FEP levels among children up to 10 years of age is not applicable to newborns (Koren et al. 1990). The measurement of the maternal and umbilical cord lead levels and FEP among 95 mother-infant pairs from Toronto showed a significant inverse correlation. Most (99%) infants had cord blood lead levels below 7 μg/dL; in 11 cases the levels were below the detection limit. The cord blood FEP levels were higher than the maternal levels. This may reflect immature heme synthesis and increased erythrocyte volume rather than lead poisoning.

An increase in urinary coproporphyrin has long been recognized in workers and children with lead poisoning and used as an indicator of excessive exposure to lead (EPA 1986a). EPA (1986a) identified a LOAEL for elevated coproporphyrin at a blood lead level of 40 μg/dL for adults and 35 μg/dL for children, but did not present the basis for this conclusion.

The threshold blood lead level for a decrease in hemoglobin in occupationally exposed adults is estimated by EPA (1986a) to be 50 μg/dL, based on evaluations of the data of Baker et al. (1979), Grandjean (1979), Lilis et al. (1978), Tola et al. (1973), and Wada et al. (1973). For example, 5% of smelter workers with blood lead levels of 40–59 μg/dL, 14% with levels of 60–79 μg/dL, and 36% with levels of >80 μg/dL had anemia. Lead-induced anemia is often accompanied by basophilic stippling of erythrocytes (Awad et al. 1986; Pagliuca et al. 1990). The blood lead threshold for decreased hemoglobin levels in children is judged to be approximately 40 μg/dL (EPA 1986a; WHO 1977), based on the data of Adebonojo (1974), Betts et al. (1973), Pueschel et al. (1972), and Rosen et al. (1974). However, a cross-sectional epidemiologic study was conducted to assess the association between blood lead level and hematocrit in 579 1–5-year-old children who lived in close proximity to a primary lead smelter that revealed that adverse effects on hematocrit may occur at even lower blood lead levels in children (Schwartz et al. 1990). Anemia was defined as a hematocrit of <35% and was not observed at lead levels below 20 μg/dL. Analyses revealed that there is a strong negative nonlinear dose-response relationship between blood lead levels and hematocrit, i.e., there was a strong association between elevation of blood lead level and the probability of anemia. Between 20 μg/dL and 100 μg/dL, the decrease in hematocrit was greater than proportional to the increase in blood lead concentration. The effect was strongest in the youngest children. The analysis also revealed that at blood levels of 25 μg/dL there is a dose-related depression of hematocrit in young children. Similarly, in a study of 200 Saudi Arabian school boys, it was found that there was a negative correlation between blood lead levels and all hematological values when the study group was subdivided into "high" blood lead (>15 μg/dL; mean 19±3 μg/dL) versus "normal" blood lead (<15 μg/dL; mean 6.5 μg/dL) (Kutbi et al. 1989). Hematocrit and mean corpuscular volume values were marginally below the normal range, red blood cells and hemoglobin were at the low normal range, and the mean corpuscular hemoglobin concentration and white blood cells were within normal range. The authors state that this pattern is predictive of the early stages of microcytic anemia, and suggest that low blood levels once considered to be safe (e.g., 25 μg/dL) may induce the early stages of microcytic anemia. However, it should be noted that both the higher and lower exposure groups had low hematological readings for all of the parameters examined in the study, and the lowest values recorded were in the lowest lead exposure group. This suggests that other factors, such as poor iron or mineral status, could be contributing to the effects reported.

Erythrocyte pyrimidine-5'-nucleotidase activity is inhibited in lead workers, with the greatest inhibition and marked accumulations of pyrimidine nucleotides apparent in workers with overt intoxication, including anemia (Paglia et al. 1975, 1977). Pyrimidine-5'-nucleotidase activity was correlated inversely with blood lead when corrected for an enhanced population of young cells due to hemolytic anemia in some of the workers (Buc and Kaplan 1978). Erythrocyte pyrimidine-5'-nucleotidase is inhibited in children at very low blood lead levels. A significant negative linear correlation between pyrimidine-5'-nucleotidase and blood lead level was seen in 21 children with blood lead levels ranging from 7 to 80 μg/dL (Angle and McIntire 1978). Similar results were seen in another study with 42 children whose blood lead levels ranged from <10 to 72 μg/dL (Angle et al. 1982). Additional findings included a direct correlation between cytidine phosphate levels and blood lead levels (log-log). There was no indication of a threshold for these effects of lead in these two studies.

Hepatic Effects. In children, exposure to lead has been shown to inhibit formation of the heme-containing protein cytochrome P-450, as reflected in decreased activity of hepatic mixed-function oxygenases (Alvares et al. 1975; Saenger et al. 1984). Two children with clinical manifestations of acute lead poisoning did not metabolize the test drug antipyrine as rapidly as did controls (Alvares et al. 1975). Significantly reduced 6 ß-hydroxylation of cortisol was observed in children who had positive calcium sodium ethylenediamine tetraacetate (EDTA) tests as compared with an age-matched control group, controlling for free cortisol (Saenger et al. 1984). These reactions are mediated by hepatic mixed-function oxygenases.

Abnormal liver function tests (alkaline phosphatase, aspartate transaminase, and gamma glutamyl transferase) and mild hepatitis revealed at necropsy were observed in a 52-year-old man who was occupationally exposed to lead following the oxyacetylene cutting of red lead painted ironwork (Pagliuca et al. 1990). The man's blood lead level upon hospital admission was 203 μg/dL. It is not clear whether this relatively high level of lead exposure is responsible for the liver toxicity observed in this man, since nothing was reported about his medical history, drinking habits, or other factors that may have contributed to hepatotoxicity.

Renal Effects. The characteristics of early or acute lead-induced nephropathy in humans include nuclear inclusion bodies, mitochondrial changes, and cytomegaly of the proximal tubular epithelial cells; dysfunction of the proximal tubules (Fanconi's syndrome) manifested as aminoaciduria, glucosuria, and phosphaturia with hypophosphatemia; and increased sodium and decreased uric acid excretion. These effects appear to be reversible. Characteristics of chronic lead nephropathy include progressive interstitial fibrosis, dilation of tubules and atrophy or hyperplasia of the tubular epithelial cells, and few or no nuclear inclusion bodies, reduction in glomerular filtration rate, and azotemia. These effects are irreversible. The acute form is reported in lead-intoxicated children, whose primary exposure is via the oral route, and sometimes in lead workers. The chronic form is reported mainly in lead workers, whose primary exposure is via inhalation. Animal studies provide evidence of nephropathy similar to that which occurs in humans, particularly the acute form (see Section 2.2.3.2).

In a study of 102 cases of occupational lead poisoning, 17 cases of clinically verified chronic nephropathy were found (Lilis et al. 1968). Endogenous creatinine clearance was <80 μg/dL. The mean blood lead level for the entire study population was 80 μg/dL (range = 42–141 μg/dL). Nephropathy was more common among those exposed to lead for more than 10 years than among those exposed for less than 10 years.

Histopathological evidence of renal damage has been observed in lead-exposed workers. Renal ultrastructure and function were examined in five men with heavy occupational exposure to lead (Cramer et al. 1974). In addition, renal function was evaluated in two men from whom renal biopsies were not obtained. Blood lead levels ranged from 71 to 138 μg/dL. Renal function tests were normal in all except for a reduced glomerular filtration rate in one worker. Two subjects with relatively short exposure to lead (6 weeks and 8 months) and blood lead levels of 89–129 μg/dL had intranuclear inclusions in the proximal tubules. Renal biopsies from workers with longer periods of lead exposure (4–20 years, blood lead levels of 71–138 μg/dL) had diffuse interstitial or peritubular fibrosis. Glomeruli were normal in all subjects. Two men exposed to lead for 15–25 years while removing old lead-based paint from a bridge also exhibited clinical and histopathological signs of nephropathy (Pollock and Ibels 1986). In one man (blood lead level = 80 μg/dL) who had two episodes of pyelonephritis over the past 11 years and hematuria, renal biopsy revealed sclerotic and obliterated glomeruli. In the other, who complained of gouty arthritis and nocturia for the past 10 years, renal biopsy revealed sclerotic glomeruli and nephronal hypertrophy with interstitial scars.

Renal function was evaluated by means of clinical, functional, and morphological studies in 11 patients diagnosed as having "plumbism" based on job background and laboratory findings (criteria not specified) (Biagini et al. 1977). Blood lead levels in these patients ranged from 50 to 200 μg/dL. Negative associations between urinary lead excretion following chelation with EDTA and clearance of p-aminohippuric acid (PAH), glomerular filtration rate and duration of lead exposure were the only statistically significant effects observed. Renal biopsies of these patients revealed signs of degeneration (swollen mitochondria, dilated endoplasmic reticulum, scanty microvilli), signs of probable regeneration (poorly differentiated cells with few microvilli, shallow infoldings of basal cell membrane), and signs of metabolic hyperactivity (intranuclear granular inclusions) in the proximal tubules. The authors concluded that chronic exposure to lead results in limited and subclinical renal effects. While this study is valuable in that histopathological evidence of lead effects on the kidney was obtained, no controls were studied, and only 11 subjects were evaluated.

In a study of lead workers, Wedeen et al. (1979) identified 15 who had no other risk factors for renal disease and who had previously unsuspected lead nephropathy (detected as reduced glomerular filtration rates). Only three of the 15 men had ever experienced symptoms of lead poisoning. Blood lead levels were as follows: >80 μg/dL in 1 subject, 40–80 μg/dL in 11 subjects, and <40 μg/dL in 3 subjects. Examination of renal biopsies from 12 of these men revealed focal interstitial nephritis in 6, in addition to nonspecific changes, including deformed mitochondria, in the proximal tubules.

Other studies where no renal biopsies were conducted have yielded varying results with regard to occupational lead exposure and nephropathy. The inconsistencies can be partially explained by differences in the renal functional parameters measured. Various indicators of renal function were assessed in 155 male lead workers and 126 male control workers (Verschoor et al. 1987). Workers were matched for factors such as age, smoking habits, socioeconomic status, and duration of employment. Parameters measured included blood lead levels, ZPP, urinary lead levels, serum creatinine, serum urea, serum uric acid, serum β_2-microglobulin, (β_2M-S), serum retinal binding protein (RBP-S), creatinine in urine, uric acid in urine, total urinary protein, urinary albumin, urinary β_2-microglobulin (β_2M-U), urinary retinal binding protein (RBP-U), immunoglobulin G, and N-acetyl-β-D-glucosaminidase (NAG). The length of exposure to lead was not explicitly stated. Exposure levels were not available, but indicators of lead body burden or effect were: blood lead level = 33.8–63.2 μg/dL in the exposed workers and 5.6–12 μg/dL in the controls; ZPP = 34–292 μmol/mol hemoglobin in the exposed workers and 10–35 μmol/mol hemoglobin in the controls. The highest blood lead level measured was 97.6 μg/dL. No significant difference between exposed and control workers was found with respect to the tubular or glomerular parameters studied, all urinary and serum parameters were within normal ranges, there was no difference in protein excretion patterns, and there were no signs of clinical renal impairment. Furthermore, no relationship was found between any of the renal parameters and duration of exposure. The NAG levels in the lead-exposed workers were significantly increased over control values, and significantly increased with increasing blood lead level and ZPP. NAG is a lysosomal enzyme that is present in renal tubular cells. It has been shown to be a sensitive indicator of early, subclinical renal disease. These results indicate that lead exposure resulting in relatively low blood levels (i.e., ≤62 μg/dL) can affect renal tubular function more so than glomerular function.

Blood lead levels, urinary lead levels, serum creatinine, blood urea nitrogen (BUN), creatinine clearance (CCT), and NAG were measured in 158 male and 51 female workers in a lead battery factory or a lead smelting plant in Japan (Ong et al. 1987). Controls consisted of 30 professional and laboratory staff members with no history of renal disease or lead exposure. The length of exposure to lead averaged 10.8±8.0 years with a range of 1–36 years. Exposure levels were not available, but indicators of lead body burden in the exposed workers were: blood lead level = 3.0–80.0 μg/dL and urinary lead level = 0.5–49.7 μg/dL. The highest blood lead level measured was 80 μg/dL, and only five workers (3%) had blood lead level levels over 60 μg/dL. Control values for these indicators of lead body burden were not provided. A weak but statistically significant positive association was found between blood lead level and BUN, blood lead level and serum creatinine, and CCT was reduced with increased blood lead level. The same associations were found with urinary lead level. The NAG levels in the lead-exposed workers were significantly increased over control values, and significantly increased with increasing blood lead level and urinary lead level (when the data were adjusted for age). These results indicate that lead exposure resulting in relatively low blood levels can affect renal function.

Various indicators of renal function were assessed in 60 workers diagnosed as having "lead poisoning" (Maranelli and Apostoli 1987). No criteria for "lead poisoning" were specified. Controls consisted of patients hospitalized for respiratory ailments with no history of lead exposure. Parameters measured included blood lead levels, urinary lead excretion following chelation with EDTA (PbU-EDTA), ZPP, urinary δ-aminolevulinic acid (ALA-U), and serum creatinine and serum uric acid clearance. The length of exposure to lead averaged 10.8±8.0 years with a range of 1–34 years, and the occupations of the workers varied considerably. Exposure levels were not available, but indicators of lead body burden or effect in the "poisoned workers" were blood lead level = 71.9±16.6 μg/dL, PbU-EDTA = 3,375±2,737 μg/24 hours, ZPP = 12.8±6.9 μg/g hemoglobin, and ALA-U = 1.4±1.2 mg/24 hours. Control values for these indicators of lead body burden were not provided. The only parameters of renal function that differed significantly from the control group were increases in BUN and serum uric acid. There was no definitive correlation between indicators of lead body burden or effect and parameters of renal function; therefore, no dose-effect relationship could be deduced from these data.

Other occupational studies have yielded negative results with regard to lead exposure and renal function. Various serum and urinary indicators of renal function were assessed in 25 male lead smelter workers and 88 male control workers (Buchet et al. 1980). Factors such as age, smoking habits, socioeconomic status, and duration of employment were examined for both groups. Parameters measured included blood lead levels, urinary lead levels, FEP, and various enzymes and proteins. The length of exposure to lead was 3.1–29.8 years. Exposure levels were not available, but indicators of lead body burden or effect were: blood lead level = 33.8–61.3 μg/dL in the exposed workers and 5.5–34.2 μg/dL in the controls; and urinary lead levels = 15.2–297.9 μg/g creatinine in the workers, 2.53–42.9 μg/g creatinine in the controls. No significant difference between exposed and control workers was found with respect to any of the parameters of renal function, and there were no signs of clinical renal impairment. FEP and ALA in urine were increased in the lead group, and the concentration of urinary ALA was found to correlate positively with blood lead levels. The results of this study indicate that exposure to lead leading to blood lead levels of ≤62 μg/dL does not result in nephrotoxicity. However, the sample included only 25 subjects.

Renal function was evaluated in a group of 36 male and 4 female lead smelter workers (Huang et al. 1988a). The workers were exposed to lead for 1–10.4 years (mean = 5.4 years). Renal function was assessed by means of a medical history, physical exam, routine urinalysis, total urinary protein, urinary IgG, β_2M-U, β_2M-S, and urinary creatinine. The presence of proteinuria is usually indicative of nephrotoxicity, increased β_2M-U without an increase in β_2M-S can indicate tubular dysfunction, and the increased excretion of IgG combined with excess total protein can indicate glomerular damage while β_2M-S levels are closely related to glomerular filtration rate. All parameters were compared to average values in the healthy Chinese from Beijing obtained in previous studies. The mean blood lead level in the exposed workers was 41.8 μg/dL and the mean urinary lead level was 71 μg/L. The only statistically significant finding was an increase in β_2M-U in the lead group. While this may indicate subclinical tubular dysfunction, the toxicological significance of this finding is not clear. Limitations of this study include a small sample size, no concurrent controls, no consideration of confounding factors such as age and smoking, and possible exposure to other toxic chemicals.

A cohort mortality study was conducted to compare the mortality rates due to chronic renal disease in 4,519 battery plant workers and 2,300 lead production or smelter workers from 1947 to 1980 (Cooper 1988; Cooper et al. 1985). The mortality data for these workers were compared with national mortality rates for white males. Environmental lead levels and blood lead levels were available for only about 30% of all workers for varying time periods from 1947 to 1972. Statistically significant increases in mortality from "other hypertensive disease" and "chronic nephritis" were seen in both lead cohorts. Limitations of this study include the fact that various confounding factors, such as smoking, were not accounted for, and the possibility that the workers were exposed to other toxic chemicals.

Taken together, these studies provide evidence for chronic nephropathy in occupationally exposed workers being associated with blood lead levels ranging from 40 to >100 μg/dL. It should be noted, however, that blood lead levels measured at the time of renal function testing may not fully reflect the exposure history that contributed to the development of chronic nephropathy in lead workers. Past exposure levels may have been higher, and the effects of the long body half-life for lead are not fully understood.

Excessive lead exposure has been implicated as a causative agent in kidney disease associated with gout (Batuman et al. 1981). A correlation was found between the amount of mobilizable lead and the degree of renal impairment in 44 veterans with gout. The 44 gout patients were similar with respect to age, duration of gout, hypertension, history of lead exposure, serum uric acid concentration, blood lead concentration, and ZPP. A 3-day EDTA lead mobilization test was administered to all 44 gout patients, and kidney function was assessed by measuring serum creatinine concentration, creatinine clearance, and 24-hour urinary protein excretion. The results of the 3-day EDTA lead mobilization test were significantly different for the gout patients with renal impairment as compared to the gout patients without renal impairment. The gout patients with renal impairment excreted 806±90 μg lead over the three days as compared to 470±52 μg lead per three days in patients with gout but no renal impairment. The upper limit of normal in this test is 600 μg lead excreted over 3 days. To rule out the possibility that the renal impairment itself was the cause of excessive mobilizable lead in patients with gout, 10 patients with renal disease but no gout were used as controls for the EDTA lead mobilization test. These controls excreted approximately the same amount of lead over the 3 days as the gout patients without renal impairment (424±72 μg lead). In addition, the severity of renal impairment (as determined by the serum creatinine concentration) was directly correlated with the amount of mobilizable lead measured in the EDTA test. It is important to note that the gout patients with high mobilizable lead and renal impairment had blood lead levels and ZPP concentrations that were no different from the rest of the group, indicating that there was no indication of lead overexposure in these individuals until the EDTA lead mobilization test was administered. Based on these results, it may be concluded that excessive lead absorption may somehow be involved in the renal impairment associated with some forms of gout.

Excessive lead exposure has also been implicated as a causative agent in kidney disease associated with essential hypertension (Batuman et al. 1983). The 3-day EDTA lead mobilization test was administered to 70 veterans; 48 had essential hypertension (27 of which also were diagnosed with essential hypertension) and the 22 that served as controls had renal failure but no hypertension. The 48 patients with essential hypertension were similar with respect to age, blood lead concentration, and history of exposure to lead. Kidney function was assessed by measuring serum creatinine concentration, creatinine clearance, and 24-hour urinary protein excretion. A significant difference was found between the hypertensive patients with renal impairment and those without with respect to the amount of mobilizable lead excreted over 3 days in the EDTA test; the patients with both hypertension and renal impairment excreted 860±101 μg lead as compared to 340±39 μg lead in the hypertensive patients without renal impairment. To rule out the possibility that the renal impairment itself was the cause of excessive mobilizable lead in patients with gout, 22 patients with renal disease but no hypertension were used as controls for the EDTA lead mobilization test. The amount of lead excreted over the 3 days by this group was not significantly different from that excreted by the hypertensive patients without renal impairment (440±50 μg lead). In addition, the severity of renal impairment (as determined by the serum creatinine concentration or creatinine clearance rate) was directly correlated with the amount of mobilizable lead measured in the EDTA test. Based on these results, it may be concluded that excessive lead absorption may somehow contribute to both the development of renal impairment and essential hypertension.

Full Fanconi syndrome has been reported to be present in some children with lead encephalopathy (Chisolm et al. 1955, Chisolm 1968). According to the National Academy of Sciences (NAS 1972), the Fanconi syndrome is estimated to occur in approximately one out of three children with encephalopathy and blood lead levels of approximately 150 μg/dL. Aminoaciduria occurs at blood lead levels >80 μg/dL in children with acute symptomatic lead poisoning (Chisolm 1962). The aminoaciduria and symptoms of lead toxicity disappeared after treatment with chelating agents (Chisolm 1962).

In a study of children with slight neurological signs indicative of lead toxicity, aminoaciduria was found in 4 of 43 children with average blood lead levels of 35 μg/dL (Pueschel et al. 1972). The highest blood lead level for the 43 children was 68 μg/dL. Although blood lead levels were not reported specifically for the children with aminoaciduria, it may be assumed that they were probably at the high end of the range.

A study of 55 adolescents who had been treated for lead intoxication in early childhood (11–17 years earlier) revealed no evidence of chronic nephropathy, as evidenced by endogenous creatinine clearance, BUN, serum uric acid, and routine urinalysis (Chisolm et al. 1976). Blood lead levels during the acute poisoning episode ranged from 100 to 650 μg/dL; all patients received immediate chelation therapy. At the time of the study, their blood lead levels had decreased to less than 40 μg/dL.

On the basis of these studies, it would appear that nephropathy occurs in children only at blood lead levels of >80 μg/dL, and usually exceeding 120 μg/dL.

Other Systemic Effects

Thyroid Effects. Limited evidence from occupationally exposed workers suggests that lead may adversely affect thyroid function (Tuppurainen et al. 1988). For example, blood lead levels, EP, total thyroxin (T_4), free thyroxin (FT_4) total triiodothyronine (T_3), and thyroid stimulating hormone (TSH) were measured in 172 Black male workers in two Kenyan car battery factories and one secondary lead smelter (Tuppurainen et al. 1988). The mean duration of exposure to lead was 7.6±5.1 years (range = 0.1–20 years). The mean blood lead level was 56±24 μg/dL (range = 15–134 μg/dL) and the mean EP was 16.3±5.1 μmol/L (range = 2–104 μmol/L). No correlation was found between blood lead level and T_4, T_3, or TSH, as determined by regression analyses. However, there was a weak, but statistically significant, negative correlation between duration of exposure and levels of T_4 and FT_4. This association was even more apparent when only workers considered to have "high" lead exposure (i.e., blood lead level of ≥56 μg/dL) were analyzed. Although these results suggest that lead may adversely affect the thyroid over time, the authors did not control for confounding factors (such as preexisting conditions that may affect thyroid function or exposure to other chemicals) and lead exposures may have varied considerably in the workers. Thus, these findings must only be considered in a limited qualitative sense.

In contrast to what has been observed in occupationally exposed adults, no effects of lead on thyroid function have been found in children. The effects of lead exposure on thyroid function in inner city children were studied (Siegel et al. 1989). Thirty-six male and 32 female children ranging in age from 11 months to 7 years (median age of 25 months) took part in the study. Blood lead levels, T_4, and T_4 uptake were determined, and sex, race, socioeconomic status, and hemoglobin were also assessed for each child. The blood lead levels ranged from 2.0 to 77 μg/dL, with a mean of 25 μg/dL. Forty-four percent of the children had elevated lead levels (>24 μg/dL). Linear regression analysis revealed that there was no association between blood lead levels and either T_4 or FT_4. This is contrary to what has been observed in adults; i.e., others have shown that there is a relationship between blood lead levels and T_4 levels in lead-exposed workers (Tuppurainen et al. 1988). The authors offered four possible explanations for the apparent lack of effect of lead on thyroid function in children. Children may be less susceptible to the toxic effects of lead on the thyroid gland. However, this is not consistent with the greater susceptibility of children to the other toxic effects of lead (e.g., neurotoxicity). The lead-exposed workers had higher blood lead levels than the children in this study (51.9 μg/dL versus 25 μg/dL). However, no effect on thyroxine was seen even in the children with blood levels of ≥60 μg/dL. The workers had a longer duration of exposure (average exposure of 7.6 years versus 2.8 years in the children). T_4 levels may not be a sensitive enough indicator of thyroid function. On the other hand, the positive findings in the adults described above are of limited value because the authors did not control for confounding factors (such as preexisting conditions that may affect thyroid function or exposure to other chemicals) and lead exposures may have varied considerably in the workers. Therefore, there is currently no compelling reason to discount the negative effects on thyroid function seen in children.

Effects on Vitamin D Metabolism. Lead appears to interfere with the conversion of vitamin D to its hormonal form, 1,25-dihydroxyvitamin D. This conversion takes place via hydroxylation to 25-hydroxyvitamin D in the liver followed by 1-hydroxylation in the mitochondria of the renal tubule by a complex cytochrome P-450 system (Mahaffey et al. 1982; Rosen and Chesney 1983). Evidence for this effect comes primarily from studies with children with high lead exposure.

Lead-exposed children with blood lead levels of 33–120 μg/dL had marked reductions in serum levels of 1,25-dihydroxyvitamin D (Rosen et al. 1980). Even in the range of 33–55 μg/dL, highly significant depressions in circulating 1,25-dihydroxyvitamin D were found, but the most striking decreases occurred in children whose blood lead levels were >62 μg/dL. In addition, children with blood lead levels of >62 μg/dL also had significant decreases in serum total calcium and ionized calcium and significant increases in serum parathyroid hormone. These conditions would tend to enhance production of 1,25-dihydroxyvitamin D, thus the inhibition caused by lead may have been greater than was indicated by 1,25-dihydroxyvitamin D levels. Serum levels of 1,25-dihydroxyvitamin D returned to normal within 2 days after chelation therapy. These results are consistent with an effect of lead on renal biosynthesis of 1,25-dihydroxyvitamin D. A strong inverse correlation between 1,25-dihydroxyvitamin D levels and blood lead was also found among children with blood lead levels ranging from 12 to 120 μg/dL, with no change in the slope of the line at levels less than 30 μg/dL (Mahaffey et al. 1982).

However, results obtained by Koo et al. (1991) indicate that low to moderate lead exposure (average lifetime blood lead level range of 4.9–23.6 μg/dL, geometric mean of 9.8 μg/dL, n=105) in young children with adequate nutritional status particularly with respect to calcium, phosphorus, and vitamin D has no effect on vitamin D metabolism, calcium and phosphorus homeostasis, or bone mineral content. The authors attribute the difference in results from other studies to the fact that the children in their study had lower blood lead levels (only 5 children had blood lead levels >60 μg/dL and all 105 children had average lifetime blood lead levels <45 μg/dL at the time of assessment) and had adequate dietary intakes of calcium, phosphorus, and vitamin D. They concluded that the effects of lead on vitamin D metabolism observed in previous studies may therefore only be apparent in children with chronic nutritional deficiency and chronically elevated blood lead levels.

Effects on Growth. Since the report by Nye (1929) of runting in overtly lead-poisoned children, a number of epidemiological studies have reported an association between blood lead levels and growth in children, who take in lead primarily through the oral route (Johnson and Tenuta 1979). However, although these findings in the early epideminiological studies were suggestive of an effect, many of the studies failed to control for possible confounding factors such as age, race, sex, or nutritional status. In addition, the more recent and better conducted epidemiological studies failed to establish an association between blood lead levels and growth.

In a recent study that considered (and ruled out) possible confounding effects of socioeconomic status on lead absorption, a set of biometric measurements (including stature and weight) for children with blood lead levels of less than 30 μg/dL and for children with blood lead levels of 40–60 μg/dL was compared (Lauwers et al. 1986). When only the children ≤8 years old were considered, the results indicated that slight decreases in biometric values occurred in the high-lead group as compared with the lower-lead group.

Stronger evidence for an association between lead exposure and growth retardation is available in the analyses by Schwartz et al. (1986) of data for 2,695 children ≤7 years old from the NHANES II study. Stepwise multiple regression analyses indicated that blood lead levels (range = 4–35 μg/dL) were a statistically significant predictor of children's height, weight, and chest circumference, after controlling for age, race, sex, and nutritional covariates. The strongest relationship was observed between blood lead and height, with segmented regression models indicating no evident threshold for the relationship down to the lowest observed blood lead level of 4 μg/dL. Parental stature was not considered as a variable, but analysis showed that age, sex, nutrition, and blood lead level accounted for 91% of the variance in height, and that the addition of blood lead to the most significant model obtained without blood lead accounted for more of the variance and was significant. The authors concluded that the mean blood lead level of the children at the average age of 59 months appeared to be associated with a reduction of approximately 1.5% in the height that would be expected if the blood lead level had been zero. The impact on weight and chest circumference was of the same magnitude. However, this study is limited in that environmental factors (in particular parental smoking) were not controlled for. This led the authors to conclude that while these findings were suggestive and pointed out a need for further research, a causal relationship could not be established.

In a preliminary report of a cohort study of Danish children of homogeneous social/ethnic background joining the first grade in 1982–1983, tooth lead was significantly associated with height after controlling for other variables (e.g., child's medical history, dietary history, behavior, tobacco smoking of parent, and sociodemographic factors) (Lyngbye et al. 1987). Exposed children had tooth lead levels of greater than 18.7 μg/g, while controls had tooth lead levels less than 5 μg/g. The average blood lead level in the exposed cohort was <60 μg/dL. The investigators concluded that early lead absorption was a risk factor for impaired growth in children. The report did not provide sufficient detail for independent evaluation of the appropriateness of this conclusion.

A retrospective study of the growth of 54 children from birth to 48 months of age was undertaken (Angle and Kuntzelman 1989). Children were initially chosen for the study based on finding high EP (>35 μg/dL) between 12 and 23 months of age. Blood lead levels were determined in these children, and the children were subdivided into two groups: the low-lead group had initial blood lead levels of <30 μg/dL (n=24), and the high-lead group had initial blood lead levels of ≥30 μg/dL (n=30). The two groups were comparable with respect to gender and skin color. None of the children were considered to have clinical signs of lead toxicity. The mean annual blood lead level increased from 17.0±1.7 μg/dL at 12–23 months to 18.5±3.5 μg/dL at 35–48 months in the low-lead group. The mean annual blood lead level decreased from 46.7±3.5 μg/dL at 12–23 months to 40.5±2.4 μg/dL at 35–48 months in the high-lead group. The mean erythrocyte protoporphyrin decreased with age in the low-lead children but remained consistently elevated in the high-lead children. The rate of weight gain was significantly increased at 15 months, and mean weight was significantly increased at 24 months in the high-lead group. Even though the high-lead children showed initial increased growth, analysis of the rates of height and weight gain from birth to 36 months showed a significant decrease in growth of high-lead children when compared to the low-lead group. The authors state that the increased growth rate at 15 months in the high-lead children is associated with increased food intake (particularly of finger foods), therefore increasing the probability of lead ingestion from dust on the fingers. The contribution of prenatal lead burden and iron deficiency to the growth patterns observed could not be determined. This study demonstrates that after an initial acceleration in growth, high blood lead may be associated with growth retardation, and that food and hand dust are among the primary sources of lead in the 1st year of life. While these results are suggestive of a correlation between weight gain and higher lead exposure at certain points in the developmental cycle, these results should be interpreted with caution because only 54 children were studied and the study was not designed for cause and effect analyses.

Two recently conducted studies failed to establish an association between blood lead levels and growth. In a study designed to look at the effect of lead exposure on stature (height and weight) among 104 lead-poisoned subjects and 27 sibling controls, blood lead did not affect growth or the genetic predisposition for eventual adult height (Sachs and Moel 1989). The lead-poisoned subjects had blood levels that ranged from 10 to 47 μg/dL, and their nonexposed sibling controls had blood lead levels that ranged from 1 to

4 μg/dL. Blood lead levels, height, and weight were measured in 1974 (the year of their first posttreatment recall for evaluation, when the mean age was 8 years) and 1985 (the year of their sixth recall, when their mean age was 18 years). Between 70% and 77% of the lead-poisoned subjects ranked in or above the 50th percentile for height in 1974, and in 1985, 84% of the lead-poisoned subjects ranked in or above the 50th percentile for height. These percentages were not different from those seen in the sibling controls.

Two sets of analyses were conducted on the data from the Cleveland Prospective Study to assess the association between blood lead levels and size from a cohort of 359 mother-infant pairs (Greene and Ernhart 1991). The first analyses investigated the association between prenatal lead exposure and neonatal size measures as well as growth through the preschool years. The second analyses were concerned with the relationships between preschool blood lead indices (at 6 months, 2 years, 3 years, and 4 years 10 months) and concurrent and subsequent measurements of weight, length, and head circumference. The possible interaction between prenatal and preschool lead exposure and its effect on reduced size were also studied. Weight, length, and head circumference were measured at birth and during five subsequent in-home visits; cord and maternal blood lead levels were used as a measure of prenatal lead exposure, and preschool blood lead samples were taken at 6 months, 3 years, and 4 years 10 months. The analyses controlled for variety of possible confounding factors. Multivariate longitudinal analyses revealed no statistically significant effect of blood lead levels on growth from birth through age 4 years 10 months.

2.2.1.3 Immunological Effects

The data on immunological effects in occupationally exposed humans following exposure to lead are inconsistent but indicate that while lead may have an effect on the cellular component of the immune system, the humoral component is relatively unaffected. Lead workers with blood lead levels of 21–90 μg/dL (median: 55 μg/dL) had more colds and influenza infections per year and had a significant suppression of secretory IgA levels (Ewers et al. 1982). Secretory IgA is a major factor in the defense against respiratory and gastrointestinal infections (Koller 1985). Serum immunoglobulin levels were not significantly altered. Immune function in lead workers exposed occupationally for 4–30 years, whose blood lead levels at the time of testing ranged from 25 to 53 μg/dL (mean = 38.4 μg/dL), was no different from controls whose blood lead levels at the time of testing ranged from 8 to 17 μg/dL (mean = 11.8 μg/dL) (Kimber et al. 1986b). There were no differences between the workers and controls with regard to serum concentrations of IgG, IgA, or IgM and no correlation between blood lead levels and serum immunoglobulin levels. In addition, response to the mitogen phytohemagglutinin (PHA) (a stimulator of T lymphocytes) and natural killer cell activity were not altered in workers compared with controls. Lymphocyte transformation (in vitro) and serum IgG and IgA levels were studied in 39 male lead storage battery workers who had exposure to lead oxides, 10 age-matched nonexposed health volunteers, and 9 nonexposed management personnel (Alomran and Shleamoon 1988). The length of exposure was not precisely specified, but the range appears to be 0–18 years. The mean blood lead level in these workers had been previously shown to be 64 μg/dL, and the concentration of lead oxide within the plant was reported to be 266 $\mu g/m^3$. No specifics were given regarding how this measurement was obtained. The lymphocytes from the exposed workers were significantly less responsive to stimulation by PHA and concanavalin A (con A) than those from the controls, and the severity of the depression was related to the duration of exposure. There was no effect on IgG and IgA levels.

Several parameters of both cellular and humoral immune function were affected in 38 lead-exposed adults as compared with 25 nonexposed controls (Coscia et al. 1987). B lymphocyte percentage and absolute count as well as absolute count of T_8 cells (with a normal T_4/T_8 ratio) were increased in the lead-exposed group as compared to the controls, and a decrease in IgM levels was observed in the lead-exposed group.

There was no correlation between blood lead levels and the cellular parameters of immunity. These results suggest that lead exposure may affect immune function in humans. However, this study is limited in that the sample size was very small (thus limiting the statistical power of the study) the level, duration, and nature of lead exposure in the experimental group varied considerably (as evidenced by the wide range of blood lead levels), there was no attempt to account for possible confounding factors in the exposed group, there is no indication that the control group was matched to the experimental group with regard to possible confounding factors, and the conclusions drawn by the authors seem unsubstantiated by the data.

The data available on the effects of lead exposure on children are very limited. In a comparison of 12 preschool children having blood lead levels ≥40 μg/dL and elevated FEP with 7 preschool children with lower blood lead levels (14–30 μg/dL), it was found that there were no differences between groups with respect to complement levels, immunoglobulin levels, or antitoxoid titers following booster immunization with tetanus toxoid (Reigart and Graber 1976). The small number of children and lack of controls limit the conclusions that can be drawn from this report.

2.2.1.4 Neurological Effects

Neurological Signs and Symptoms in Adults. The most severe neurological effect of lead in adults is lead encephalopathy, which is a general term to describe various diseases that affect brain function. Early symptoms that may develop within weeks of initial exposure include dullness, irritability, poor attention span, headache, muscular tremor, loss of memory, and hallucinations. The condition may then worsen, sometimes abruptly, to delirium, convulsions, paralysis, coma, and death (Kumar et al. 1987). Histopathological findings in fatal cases of lead encephalopathy in adults are similar to those in children (see discussion below).

Severe lead encephalopathy is generally not observed in adults except at extremely high blood lead levels (e.g., 460 μg/dL, [Kehoe 1961a]). Other data (Smith et al. 1938) suggest that acute lead poisoning, including severe gastrointestinal symptoms and/or signs of encephalopathy, can occur in some adults at blood lead levels that range from approximately 50 to >300 μg/dL, but the data are somewhat ambiguous.

Occupational exposure to lead has often been associated with subjective signs of neurotoxicity. The literature contains numerous case reports and small cohort studies that describe a higher incidence of these subjective symptoms, including malaise, forgetfulness, irritability, lethargy, headache, fatigue, impotence, decreased libido, dizziness, weakness, and paresthesia at blood lead levels that range from approximately 40 to 120 μg/dL following acute-, intermediate-, and chronic-duration occupational exposure (Awad et al. 1986; Holness and Nethercott 1988; Marino et al. 1989; Matte et al. 1989; Pagliuca et al. 1990; Pasternak et al. 1989; Pollock and Ibels 1986; Schneitzer et al. 1990). For example, significantly increased central and peripheral nervous system and gastrointestinal symptoms were reported among 25 lead workers with maximum blood lead levels of 50–69 μg/dL and significantly increased central nervous system symptoms among 20 lead workers with maximum blood lead levels <50 μg/dL (Haenninen et al. 1979). Referent controls (n=23) had average blood lead levels of 11.9 μg/dL. In another study, no smelter workers with blood lead levels of <40 μg/dL had signs or symptoms of lead intoxication, while 13% of the workers with blood lead levels of 40–79 μg/dL had extensor muscle weakness or gastrointestinal symptoms (Baker et al. 1979).

A study comparing 288 lead-exposed workers (current or historical blood lead level of >35 μg/dL) at three battery plants with 181 unexposed workers (current blood lead level of ≤35 μg/dL) at a truck frame plant reported a few differences in neurobehavioral or psychosocial indices (Parkinson et al. 1986). Because the lead-exposed workers were younger, less educated, employed for fewer years, and earned less income than the unexposed workers, the analysis adjusted for age, education, and income. Exposed workers had mean current, time-weighted average and peak blood lead levels of 40.0, 48.8, and 78.8 μg/dL, respectively. Blood lead data for unexposed workers were not characterized in this manner. Exposed workers had an increase in the number of work-related accidents and poorer performance in a motor speed/manual dexterity test with the nondominant hand, and greater levels of conflict in interpersonal relationships as compared with unexposed workers. When multiple regression analyses were performed on the data for exposed workers, only the levels-of-conflict measure showed a significant dose-response relationship with current or cumulative blood lead levels.

Twenty unexposed men (mean blood lead level = 20.4 μg/dL; range = 11.1-27.1 μg/dL), 20 men exposed to low lead levels (mean blood lead level = 31.7 μg/dL; range = 26–35 μg/dL), and 20 men exposed to high lead levels (mean blood lead level = 52.5 μg/dL; range = 45–60 μg/dL) at an electric storage battery plant were studied (Campara et al. 1984; Zimmerman-Tansella et al. 1983). Consistent and significant dose-response trends were observed in symptoms such as loss of appetite, paresthesia in lower limbs, weakness of upper limbs, and dropping of objects, with the most marked increases in neurological symptoms in the high-lead group (Zimmerman-Tansella et al. 1983). In addition, the high-lead workers performed significantly less well on neurobehavioral tests, with general performance on cognitive and visual-motor coordination tasks and verbal reasoning ability most markedly impaired (Campara et al. 1984).

The results of these studies showing neurological effects at lower exposure levels of lead indicate that the lowest levels for overt signs and symptoms of neurotoxicity in adults is in the range of 40–60 μg/dL. These neurological signs and symptoms occur at roughly the same blood lead levels as do other overt signs and symptoms of lead intoxication, such as gastrointestinal complaints.

Behavioral Function in Adults. Neurobehavioral testing has revealed effects in adults at blood lead levels below those causing encephalopathy (i.e., 40–80 μg/dL). Evaluations of occupationally exposed adults include several affected parameters at blood lead levels between 40 and 80 μg/dL. Disturbances in oculomotor function (saccadic eye movements) in lead workers with mean blood lead levels of 57–61 μg/dL were reported in a study by Baloh et al. (1979) with follow-up by Spivey et al. (1980) and in a study by Glickman et al. (1984). Deficits in hand-eye coordination and reaction time were reported in 190 lead-exposed workers (mean blood lead level = 60.5 μg/dL) (NIOSH 1974). Most of the workers had been exposed for between 5 and 20 years. A similar study, however, reported no differences in arousal, reaction time, or grip strength between controls (mean blood lead level = 28±10 μg/dL) and workers who had been exposed to lead for 12±9.5 years (mean blood lead level = 61±12 μg/dL) (Milburn et al. 1976). Disturbances in reaction time, visual motor performance, hand dexterity, IQ test and cognitive performance, nervousness, mood, or coping ability were observed in lead workers with blood lead levels of 50–80 μg/dL (Arnvig et al. 1980; Haenninen et al. 1978; Hogstedt et al. 1983; Mantere et al. 1982; Valciukas et al. 1978). As previously noted, Campara et al. (1984) found that workers with blood lead levels of 45–60 μg/dL performed less well on neurobehavioral tests. Impaired memory and learning ability were observed in workers with time-weighted average blood lead levels of 27–52 μg/dL (Hogstedt et al. 1983). In another study, impaired verbal concept formation, memory, and visual/motor performance and increased rates of depression, confusion, anger, fatigue, and tension were found among workers with blood lead levels of >40 μg/dL (Baker et al. 1983). No neurobehavioral effects were seen in 288 randomly selected males who were occupationally exposed to lead as compared to 181 demographically similar controls (Ryan et al. 1987). The mean blood lead level in the exposed workers was 40.1 μg/dL and that of the controls was 7.2 μg/dL. Nineteen tests of neuropsychological performance were conducted. The lead-exposed workers performed no differently from controls on all measures except psychomotor speed and manual dexterity.

The authors discounted this difference due to the observation that conflicting results were obtained in two different tests of motor speed and manual dexterity and possible confounding effects of age. There was no evidence that history of previous very high exposure had any effect on performance. This study was well conducted; the study design was good, the statistical analyses were appropriate, and potential confounders (i.e., education, age, alcohol consumption, exposure to other toxicants) were taken into account.

Ninety-one workers divided into three groups based on blood lead levels (<20 μg/dL, 21–40 μg/dL, 41–80 μg/dL) underwent a battery of neuropsychological testing including syntactic reasoning, serial reaction time, category search, visual spatial memory, and category search recall (Stollery et al. 1989). They also completed a mood checklist. There was no significant difference in mood in the three exposure groups. Workers with high blood lead concentrations showed evidence of impairment on tests of serial reaction time and category search, with only weak impairment on tasks measuring syntactic reasoning and delayed verbal free recall. In general, the magnitude of the impairment correlated with blood lead levels. The impairment of serial reaction time was the best predictor of blood lead levels. Limitations of this study include the fact that there were no lead-free controls, subjects had variable durations of exposure, and only cross-sectional exposure data were available (i.e., no history of blood lead levels in the past were available).

One study has reported effects on neurobehavioral function in lead-exposed workers at mean blood levels of 50 μg/dL (Williamson and Teo 1986). Neurobehavioral function was measured using tests that are based on information processing theory in 59 lead workers and 59 controls matched for age, type of job, time on the job, education level, smoking history, and alcohol consumption. Statistically significant decreases in the lead-exposed workers were seen for critical flicker fusion reaction, simple reaction time, tracking speeds, hand steadiness tests, and sensory store memory. Sensory store memory speed showed a low but statistically significant correlation with blood lead concentrations. Measurements of neurobehavioral function seemed well chosen, and repeated measures with associated appropriate statistics were used. The performance of the lead-exposed workers was significantly impaired. The critical flicker fusion threshold may reflect retinal or intermediate visual pathway function as well as cortical arousal.

In summary, in studies where adults were exposed occupationally to lead, a number of neurobehavioral parameters were affected. Blood lead levels in these workers were between 40 and 80 μg/dL.

<u>Peripheral Nerve Function in Adults</u>. There are numerous studies available on peripheral nerve function that measured the conduction velocity of electrically stimulated nerves in the arm or leg of lead workers. Several studies will be summarized here. In prospective occupational studies, decreased nerve conduction velocities (NCVs) were found in workers with blood lead levels of 30–48 μg/dL (Seppalainen et al. 1983), whereas another study found no significant differences in NCVs in workers with blood lead levels of 60–80 μg/dL, relative to controls (Spivey et al. 1980). Decreased NCVs were seen in the median (motor and sensory) and ulnar (motor and sensory) nerves of newly employed high-exposure workers after 1 year of exposure and in the motor nerve conduction velocity of the median nerve of this group after 2 or 4 years of exposure (Seppalainen et al. 1983). Although the severity of the effects on NCV appeared to lessen with continued exposure, several of the high-exposure workers in this study quit 1 or 2 years after starting. Thus, the apparent improvement in NCVs may have been due to a healthy worker effect. A similar healthy worker effect may have accounted for the negative results of Spivey et al. (1980) who tested ulnar (motor and slow fiber) and peroneal (motor) nerves in 55 workers exposed for 1 year or more. Davis and Svendsgaard (1990), on the other hand, concluded that the results of these two studies ". . . are not as inconsistent as they may appear." The studies differed in design; one prospectively obtained exposure history, while the other did it retrospectively. The end points that were measured also differed;

Spivey et al. (1980) did not test the median nerve, which was the most sensitive endpoint in the study by Seppalainen et al. (1983).

In cross-sectional occupational studies, significant decreases in NCVs were observed in fibular (motor) and sural (sensory) nerves as a function of blood lead levels with duration of exposure showing no effect (Rosen et al. 1983). In another study, decreases in NCVs of ulnar (sensory, distal) and median (motor) nerves were seen primarily at blood lead levels of >70 μg/dL (Triebig et al. 1984). Duration of exposure and number of lead-exposed workers in these two studies were 0.5-28 years and 15 workers (Rosen et al. 1983), and 1-28 years and 133 workers (Triebig et al. 1984). The study of Araki et al. (1980) indicates that the decrease in NCV is in fact due to lead; median (motor) NCVs in workers with a mean blood lead level of 48.3 μg/dL were improved significantly when blood lead levels were lowered through $CaNa_2EDTA$ chelation therapy.

There is suggestive evidence indicating that the changes in NCV associated with lead exposure may be transient. Muijser et al. (1987) investigated the effects of a limited (5-month) exposure to lead during the demolition of a steel structure coated with lead-based paints. The motor and sensory nerve conduction velocities were measured in the median and ulnar nerves of eight exposed workers and compared with unexposed referents as well as themselves at 3 and 15 months after the termination of exposure. The mean blood lead levels in the exposed workers were 82.5 ± 18.9 μg/dL at the termination of exposure, 50.3 ± 9.9 μg/dL 3 months after the termination of exposure, and 29 ± 11.8 μg/dL 15 months after the termination of exposure. Following termination of the exposure, the motor nerve conduction velocity and distal motor latency were slowed as compared to the referents. However, the distal sensory conduction velocity was not affected by lead exposure. Three months after exposure, these affected parameters showed improvement, and 15 months after exposure were not different from the referents. These results suggest that a limited (5-month) exposure to lead results in NCV deficits that are specific to motor nerves and are reversible in nature.

The results of these studies indicate that NCV effects occur in adults at blood lead levels <70 μg/dL, and possibly as low as 30 μg/dL. Ehle (1986), in reviewing many of the studies of NCV effects, concluded that a mild slowing of certain motor and sensory NCVs may occur at blood lead levels below 60 μg/dL, but that the majority of studies did not find correlations between blood lead and NCV below 70 μg/dL and that slowing of NCV is neither a clinical nor a subclinical manifestation of lead neuropathy in humans. Ehle (1986), however, did not cite or analyze the studies by Rosen et al. (1983) or Seppalainen et al. (1983). Other reviewers have pointed out that decreases in NCV are slight in peripheral neuropathies (such as that induced by lead) that involve axonal degeneration (Le Quesne 1987), and that although changes in conduction velocity usually indicate neurotoxicity, considerable nerve damage can occur without an effect on conduction velocity (Anderson 1987). EPA (1986a) noted that although many of the observed changes in NCV may fall within the range of normal variation, the effects represent departures from normal neurological functioning. NCV effects are seen consistently across studies and although the effects may not be clinically significant for an individual, they are significant when viewed on a population basis. This is further supported by the meta analysis of effects of lead exposure on NCV conducted by Davis and Svendsgaard (1990). These authors concluded: "Whatever the ultimate explanation for the lack of a simple relationship between NCV and blood lead, it seems that NCV effects are a function of lead exposure, although not necessarily blood lead level. The imprecision of blood lead may account for the mixed results that various studies have produced . . ."

Neurological Signs and Symptoms in Children. High-level exposure to lead produces encephalopathy in children. The most extensive compilation of dose-response information on a pediatric population is the summarization by NAS (1972) of unpublished data from the patient populations reported in Chisolm (1962, 1965) and Chisolm and Harrison (1956). This compilation relates the occurrence of acute encephalopathy and death in children in Baltimore to blood lead levels determined by the Baltimore City Health Department between 1930 and 1970. Other signs of acute lead poisoning and blood lead levels formerly regarded as asymptomatic were also summarized. An absence of signs or symptoms was observed in some children at blood lead levels of 60–300 μg/dL (mean = 105 μg/dL). Acute lead poisoning symptoms other than signs of encephalopathy were observed at blood lead levels of approximately 60–450 μg/dL (mean = 178 μg/dL). Signs of encephalopathy such as hyperirritability, ataxia, convulsions, stupor, and coma were associated with blood lead levels of approximately 90–800 μg/dL (mean = 330 μg/dL). The distribution of blood lead levels associated with death (mean = 327 μg/dL) was virtually the same as for levels associated with encephalopathy.

Additional evidence from medical reports (Bradley and Baumgartner 1958; Bradley et al. 1956; Gant 1938; Rummo et al. 1979; Smith et al. 1983) suggests that acute encephalopathy in the most susceptible children may be associated with blood lead levels in the range of 80–100 μg/dL.

Histopathological findings in fatal cases of lead encephalopathy in children include cerebral edema, altered capillaries, and perivascular glial proliferation. Neuronal damage is variable and may be caused by anoxia (EPA 1986a).

Numerous studies clearly show that childhood lead poisoning with encephalopathy results in a greatly increased incidence of permanent neurological and cognitive impairments. Additional studies indicate that children with symptomatic lead poisoning without encephalopathy (blood lead level = >80–100 μg/dL) also have an increased incidence of lasting neurological and behavioral damage.

<u>Behavioral Function in Children</u>. A number of studies of asymptomatic children with relatively high lead body burdens have been published. These children were identified through lead screening programs or other large-scale programs focusing on mother-infant health relationships and early childhood development. Studies that were conducted rigorously enough to warrant consideration of their findings were those of de la Burde and Choate (1972, 1975), Ernhart et al. (1981), Kotok (1972), Kotok et al. (1977), and Rummo et al. (1979). These studies found that, in general, groups with high lead exposure performed less well on IQ or other psychometric tests than did referent control groups with lower lead exposures. Some of these studies did not control for important confounding variables, such as parental IQ or educational background; when reanalyzed taking these variables into account, the authors found that differences between lead-exposed and control children were reduced or lost statistical significance. In addition, many of the referent control groups tended to have what are now recognized to be elevated blood lead levels (averaging 20–40 μg/dL, or 55 μg/dL in the case of Kotok [1972]). Nevertheless, the consistent pattern of lower IQ values and other neuropsychologic deficits among the children exposed to higher lead levels in these studies indicates that cognitive deficits occur in apparently asymptomatic children with markedly elevated blood lead levels (starting at 40–60 μg/dL and ranging up to ≥70–200 μg/dL).

The average decrement of approximately 5 IQ points observed in studies by de la Burde and Choate (1972), and Rummo et al. (1979), described in more detail below, represents a reasonable estimate of the magnitude of full-scale IQ decrements associated with markedly elevated blood lead levels (mean: approximately 50–70 μg/dL) in asymptomatic children.

A mean Stanford-Binet IQ decrement of 5 points, fine motor dysfunction, and altered behavioral profiles were found in 70 preschool children exhibiting pica for paint and plaster and elevated blood lead levels

(>40 μg/dL, mean of 58 μg/dL), when compared with results for matched control subjects not engaged in pica for paint and plaster (de la Burde and Choate 1972). A follow-up study on these children (ages 1-3 years) at 7-8 years of age (de la Burde and Choate 1975) reported a mean Wechsler Intelligence Scale for Children (WISC) full-scale IQ decrement of 3 points and impairment in learning and behavior, despite decreases in blood lead levels since the original study. These studies, however, did not report the blood lead levels in controls.

Additional evidence of lead-induced decrement in children's IQ was provided by Rummo et al. (1979) who observed hyperactivity and a decrement of approximately 16 IQ points on the McCarthy General Cognitive Index (GCI) among children who had previously had encephalopathy and whose average maximum blood lead levels at the time of encephalopathy were 88 μg/dL (average blood lead level = 59-64 μg/dL). Asymptomatic children with long-term lead exposures and average maximum blood lead levels of 68 μg/dL (average blood lead level = 51-56 μg/dL versus 21 μg/dL in controls) had an average decrement of 5 IQ points on the McCarthy GCI. Their scores on several McCarthy Subscales were generally lower than those for controls, but the difference was not statistically significant (at $p<0.05$). Children with short-term exposure and average maximum blood lead levels of 61 μg/dL (average blood lead level = 46-50 μg/dL) did not differ from controls. Blood lead levels in controls did not exceed 40 μg/dL (maximum: 23 μg/dL). In these studies, the environmental exposure levels and the durations of lead exposure were not reported.

A number of general population studies available evaluated asymptomatic children with lower lead body burdens than those evaluated in the above studies. Some of these studies provide evidence of an association between neurobehavioral effects and the relatively low body burdens of lead representative of general pediatric populations. The effects of blood lead on IQ may have major implications for public health when considered on a population basis as discussed by Davis and Svendsgaard (1987) and Grant and Davis (1989). However, the practical meaning of a 4-5-point decrement in IQ for the individual may be insignificant. A study of 158 first- and second-grade children by Needleman et al. (1979) provides acceptable evidence for the association of full-scale IQ deficits of approximately 4 points and other neurobehavioral defects with tooth dentin lead values that exceed 20-30 ppm. Corresponding average blood lead values would probably range from 30 to 50 μg/dL (EPA 1986a). In comparison with children having low dentin lead levels (<10 ppm), children having high dentin lead levels (>20 ppm) had significantly lower full-scale WISC-Revised scores; IQ deficits of approximately 4 points; and significantly poorer scores on tests of auditory and verbal processing, on a test of attentional performance as measured by reaction time under conditions of varying delay, and on a teachers' behavioral rating. The frequency of non-adaptive classroom behavior as rated by teachers increased in a dose-related fashion to dentin lead levels (Needleman et al. 1979). The distribution of verbal IQ scores was shifted downward in the high-lead group, such that none of the children in the high-lead group had verbal IQ scores of >125, whereas 5% of the children in the low-lead group had verbal IQ scores of >125. Furthermore, children in the high-lead group were three times more likely to have verbal IQ scores of <80 than were children in the low-lead group. Using regression analysis, Bellinger and Needleman (1983) found that IQ scores of children in the high-lead group (with >20 ppm dentin lead) fell below those expected based on their mothers' IQ scores and that the amount by which a child's IQ fell below the expected IQ increased with increasing dentin lead levels in what appeared to be a nonlinear manner. These data indicate that dentin lead level was not significantly correlated with IQ residuals in the low-lead children (with >10 ppm dentin lead) or in the high-lead children (with 20-29.9 ppm dentin lead) but was significantly correlated with IQ residuals in high-lead children with 30-39.9 ppm dentin lead.

The study by Needleman et al. (1979) has been reanalyzed in additional reports (Bellinger and Needleman 1983; Needleman et al. 1985) and critically evaluated by EPA, as well as by other investigators. It was pointed out that the teacher's ratings of classroom behavior were rather weak; no information was provided on reliability and validity of the properties on the scale.

In a later study, a subset (n=132) of a cohort of children studied as primary school students was reexamined as young adults (mean age = 18.4 years) (Needleman et al. 1990). Neurobehavioral functioning had been found to be inversely related to dentin lead levels at the earlier examination (see discussion above). When the 132 were reexamined 11 years later, impairment of neurobehavioral function was still found to be related to the lead content of teeth shed at the ages of 6 and 7 years. In this study, higher lead levels in childhood were significantly associated with lower class standing in high school, increased absenteeism, lower grammatical-reasoning scores, lower vocabulary, poorer hand-eye coordination, longer reaction times, and slower finger tapping. However, no significant associations were found with the results of 10 other tests of neurobehavioral functioning. One problem with this study is that these later effects could stem from a poor academic start as opposed to effects of lead exposure. It is a well-known fact that early failure in school is a good predictor of later failure in school. Although this study used appropriate statistical methods for analyses and was controlled for several potential confounders, it has been criticized for problems similar to those of the Needleman et al. (1979) study.

Other investigators have also found that parameters of neurobehavioral function are associated with tooth lead levels. A cross-sectional cohort of school children in first grade was ascertained in the city of Aarhus, Denmark (Hansen et al. 1989). The population is very homogeneous with regard to ethnicity and language. A total of 2,412 children were contacted and asked to contribute a shed deciduous tooth. A total of 1,291 children responded (response rate = 54%). Lead was determined in the circumpulpal dentin and averaged 10.7 μg/g. A nested case-control study was set up within this cohort. Children with lead levels above 18.7 μg/g (n=110) were matched by sex and socioeconomic status with children with levels <5.0 μg/g in order to identify risk factors for exposure to lead. The cases and controls were reviewed and excluded if medical risk factors for neurobehavioral effects were present. Psychometric tests were administered to 162 children. The high-lead children scored lower on the WISC than the low-lead controls. No significant difference was seen between the high- and low-exposure groups on the Performance IQ and on several experimental tests. Impaired function associated with lead exposure was also found on the Bender Visual Motor Gestalt Test ($p<0.001$) and on a behavioral rating scale ($p<0.01$). These results suggest that although low lead levels do not cause severe intellectual reduction, some children may be affected in neuropsychological functioning at low levels seen in minimally polluted areas.

The relationship between current and long-term indicators of lead exposure was studied to establish which indicator correlated best with psychometric test scores, and to determine the most suitable neurological test to evaluate the early effects of low-level lead exposure (Bergomi et al. 1989). Children (131 males and 106 females) whose average age was 7 years 8 months living in an area of northern Italy with a high density of ceramics factories were chosen. The daily air levels of lead decreased from 2.4–3.8 $\mu g/m^3$ in 1975 to 0.20–1.81 $\mu g/m^3$ in 1985, the year of the study. The biological indicators of lead exposure measured in this study were blood lead, tooth lead, hair lead, and ALAD activity. The following psychometric tests were conducted: WISC-Revised IQ, including two verbal and two performance tests; Bender Gestalt test to assess visual-motor performance; Trail Making test to evaluate visual-motor and sequential ability; Toulouse Pieron cancellation test to evaluate ability in figure identification, discrimination, and attention; and a test for delayed reaction time. The influence of potentially confounding variables (e.g., age, sex, and parental socioeconomic status) were evaluated and accounted for in the regression analyses that were performed. Higher levels of hair and tooth lead and the IQ test were found to be affected by the socioeconomic status. The geometric means of blood lead, hair lead, and tooth lead were 11.0 μg/dL, 6.8 μg/g, and 6.1 μg/g, respectively. Mean ALAD activity was 51 milliunits (mU)/mL red blood cells. Statistical analyses revealed that total and verbal WISC-R IQ and Toulouse Pieron test results were negatively correlated with levels of lead in teeth. ALAD values were also related to WISC-R IQ scores. The most predictive measure of lead exposure was tooth lead (which is indicative of chronic lead exposure). Blood lead (which is indicative of current exposure) and hair lead (which is indicative of short-term exposure) were of little or no predictive value. These results indicate that neuropsychological impairment is associated with long-term lead exposure. Limitations of this study include the fact that no controls were used.

One-hundred and four children of lower socioeconomic status were evaluated on the Bayley Mental Development Index (MDI) or Stanford-Binet IQ Scale at ages 10 months to 6.5 years by Schroeder et al. (1985) and Schroeder and Hawk (1987). Hierarchical backward stepwise regression analyses indicated that blood lead levels (range: 6–59 μg/dL) were a significant source of the variance in IQ and MDI scores after controlling for socioeconomic status and other factors. Fifty of the children were examined again 5 years later, at which time blood lead levels were ≤30 μg/dL. The 5-year follow-up IQ scores were inversely correlated with contemporary and initial blood lead levels, but the effect of lead was not significant after covariates, especially socioeconomic status, were included in the analysis.

The above study was replicated later with 75 asymptomatic Black children, 3–7 years old, of uniformly low socioeconomic status (Hawk et al. 1986; Schroeder and Hawk 1987). Backward stepwise multivariate regression analysis revealed a highly significant negative linear relationship between Stanford-Binet IQ scores and contemporary blood lead levels over the entire range of 6–47 μg/dL (mean = 20.8 μg/dL). The association was nearly as striking when past maximum or mean blood lead levels were used. Because socioeconomic status was uniformly low, it was not a significant covariate. These results indicate that it may be much easier to detect the effects of lead from a group of homogenous socioeconomic background and to tell more about the nature of susceptibility.

More recently, a total of 501 children, 6–9 years old, and of higher and less uniform socioeconomic status, from Edinburgh, Scotland, exposed to lead primarily via drinking water were examined by Fulton et al. (1987). The children were selected from a larger sample of 855 (mean blood lead level = 10.4 μg/dL) by taking all subjects in the top quartile of the blood lead distribution from each of the 18 participating schools plus a random approximately 1 in 3 subsample of the remaining children. The mean blood lead level of the study population was 11.5 μg/dL, with a range of 3.3–34 μg/dL. A blood lead level >25 μg/dL was found in 10 children. Multiple regression analyses revealed a significant inverse correlation between log blood lead and the British Ability Scales Combined (BASC) score and attainment test scores for number skills and word reading after adjustment for confounding variables. Further analysis divided the children into 10 groups of approximately 50 each based on blood lead level and plotted the group mean lead values against the group mean difference from the school mean score, adjusted for covariates. The authors reported that this analysis revealed a dose-effect relationship extending from the mean blood lead level of the highest lead groups, 22.1 μg/dL, down through the mean blood lead level of the lowest-lead group, 5.6 μg/dL, without an obvious threshold. This study provides evidence that blood lead levels of less than 25 μg/dL may result in IQ deficits.

Two recent studies reported findings at even lower blood lead levels. Wang et al. (1989) reported on school children residing near a battery plant in Shanghai, China. A significant dose-effect relationship was found between children's blood lead levels and their neuropsychological performance without any obvious signs of lead poisoning. The blood levels in these children (6–14 years old) ranged from 10 to >30 μg/dL; IQ decreased as blood lead level increased. This dose-response existed after confounding variables were controlled. However, no non-lead-exposed group was used. The study estimated that an increase of

10 μg/dL of blood lead would result in a lowering of verbal IQ of 8 points, performance IQ of 7 points, and full-scale IQ of 9 points.

In the second study Silva et al. (1988) evaluated intelligence, reading and behavior problems in 579 11-year-old children in New Zealand. Mean blood lead levels were 11.1 μg/dL (range: 4-50 μg/dL). The authors found a significant increase in behavior problems (inattention and hyperactivity) with increased blood lead levels.

On the other hand, several studies have been published that suggest that there is no association between blood lead levels and neurobehavioral development (Cooney et al. 1989a; Ernhart et al. 1990; Harvey et al. 1984, 1988; Lansdown et al. 1986; McMichael et al., 1986; Pocock et al. 1989; Smith et al. 1983), or that the effects are not permanent (Dietrich et al. 1987a, Bellinger et al. 1989a). A cohort of Australian children was investigated in a study that was designed to test the hypothesis that low-level ambient lead exposure in the prenatal or early postnatal periods affects mental or motor development at age 4 (Cooney et al. 1989a). Stringent selection criteria were used to ensure a homogeneous sample (n=207) so that potential confounders could be minimized and the statistical power of the study enhanced. Blood lead levels were obtained at birth (cord blood), at 6-month intervals to 4 years, and again at 5 years. This sample was drawn from a well-educated, middle-class population. Mean blood lead levels increased from birth to 18 months, then steadily declined to 48 months. At 42 months, the percentage of the sample reaching the Australian level of concern (25 μg/dL) was 1.5%; at 48 months, this percentage was 0.5%. The geometric mean blood lead level at 48 months was 10.1 μg/dL. This study found no association between current or any previous blood lead level with any developmental outcomes at age 4. These findings indicate that blood lead levels around 10 μg/dL have little or no effect on neurobehavioral development at age 4. This study was well designed and the statistics were thorough and appropriate. The selection criteria did produce a homogeneous well-educated, middle-class sample, so these results may not be extrapolated to other populations. Several prospective studies that focussed on neurobehavioral effects of prenatal exposure to lead are summarized in Section 2.2.1.5.

Eighteen separate measures were made on a total of 201 boys and girls aged 5.5 years to assess a variety of cognitive, performance, neuropsychological, and behavioral end points (Harvey et al. 1988). The children were randomly selected from birth records from the inner city area of Birmingham, United Kingdom. The selection criteria were quite stringent to control for confounding factors in neuropsychological development. There were no significant correlations between blood lead and any of the three IQ measures. Birth order and mother's IQ were good predictors of IQ. The Factual Performance Test time decreased with increasing blood lead levels (an improvement in performance), but results of the star copying test were poorer as lead levels increased. The authors concluded that the effects of lead found in this inner urban area (mean blood lead = 13.05 μg/dL) in the United Kingdom are small and generally not significant.

Results by Smith et al. (1983), indicated an association between lead burden (mean blood lead = 12.8 μg/dL; range = 7–27 μg/dL) and intelligence in 6-year-old children in London. However, no association between blood lead levels and intelligence and other psychological tests remained once social factors were controlled. Lansdown et al. (1986) conducted an investigation in children of the same age, living near a main road in London. In these children, the mean blood lead level was 12.75 μg/dL (range = 7–24 μg/dL). The authors found no evidence of the previously observed original association, which may have been due to different social compositions of the two groups. The second study group consisted of more middle-class families than the first group.

Pocock et al. (1989) further investigated the influence of confounding factors (sex, social group, family size, length of gestation, birth weight, hospital stay after birth, mother's IQ and mental health, parent's marital relationship and interest in child, and family characteristics score) in addition to lead that may impact upon children's IQ. The investigators used the cohort from the study by Smith et al. (1983). Body burden of lead was determined by lead concentration in teeth (low = 2.5 μg/g; medium = 5.5 μg/g; and high = >8 μg/g). Rather than dividing the children into groups of low, medium, and high lead concentration, the actual tooth concentration was used as a continuous variable. When all factors were considered, parental IQ was the best predictor for child IQ along with family size, social class, and quality of marital relationship. Tooth lead concentration was not associated with child IQ.

The studies by Ernhart et al. (1988) and Ernhart and Greene (1990) are described in detail in the chapter on developmental effects of lead. In these studies, no associations were found between prenatal lead exposure and intelligence or language development. The studies by Dietrich et al. (1987a) and Bellinger et al. (1989a), also described in the developmental chapter, demonstrated that any effects that may have been present early in life were no longer present after 2 years.

In conclusion, blood lead levels of 40–60 μg/dL are considered to be markedly elevated in children, and the neurobehavioral effects that have been demonstrated at these levels are generally accepted. There are no clear definitions of what constitutes low versus moderate blood lead levels, and effects observed at the lower levels (particularly <15 μg/dL), have proven more difficult to separate from socioeconomic and other variables. Many of the cross-sectional studies that showed neurobehavioral and other deficits, did so at mean blood lead levels of >15 μg/dL. The studies that used dentin lead as an indicator of exposure, mostly fall into this category of exposure level. Two recent well-designed studies (Fulton et al. 1987; Silva et al. 1988) demonstrated effects on behavior, number skills, and word reading at mean blood lead levels in children as low as 11 μg/dL. Earlier studies by McBride et al. (1982) and Winneke et al. (1984) showed no effects on intelligence at blood lead levels of 14 and 8 μg/dL, respectively. A meta-analysis of 13 studies (providing data on an inverse relationship between blood lead and children's IQ) concluded that the joint probability of obtaining the reported results was less than 3 in a billion (Needleman 1987b; Needleman and Bellinger 1989). This study indicates that the effects observed at the lower levels of blood lead are real and do not constitute findings by chance.

Suggestive evidence of a lead-related decrease in hearing acuity in children has been reported by Robinson et al. (1985) and Schwartz and Otto (1987). Hearing thresholds at 2,000 Hertz increased linearly with maximum blood lead levels, indicating that lead adversely affects auditory function. The blood lead levels in 75 asymptomatic Black children, 3–7 years old, ranged from 6 to 59 μg/dL (mean = 26.7 μg/dL). The children were healthy and did not have middle ear infections at the time of testing.

NHANES II data, including audiometric results, developmental milestones (age at which a child first sat up, walked, and spoke, according to parent's recollection) and presence of hyperactivity and speech difficulties in 4,519 children (4–19 years old) were analyzed by Schwartz and Otto (1987). The analyses included possible covariates or confounding variables that were then available from NHANES II data (e.g., race, sex, head of household, education level, income, dietary factors, indices of iron deficiency and anemia [for developmental milestones], history of signs of ear infection [for audiometric results]). Because children's blood lead levels decrease with age but tend to remain in the same percentile within age group, data were analyzed in two different ways: one with current blood lead as an independent variable and the other with blood lead percentile rank within age group as an independent variable. Logistic regression analysis revealed that the probability of elevated hearing thresholds for both ears at 500, 1,000, 2,000, and 4,000 Hertz increased significantly with increasing blood lead levels; this relationship was apparent across the entire range of blood lead levels from <4 to >50 μg/dL. When the regression analysis used blood lead percentile rank within age group as the independent variable, the association with hearing was not significant. According to the investigators, the lack of association with lead rank indicated that the effect of lead was due to current rather than past lead exposure. The probability that a child was hyperactive increased significantly with increasing blood lead levels (as blood lead percentile rank within age group). The probability of speech impairment, however, was not related to blood lead levels. Linear regression analysis demonstrated that blood lead levels (as blood lead percentile rank within age group) were significantly associated with delays in all three developmental milestones.

These two studies indicate that exposure to low levels of lead may impact negatively upon children's hearing. However, the authors of the Robinson study did not state whether age and other possible confounding variables were controlled for. Similarly, in the NHANES study, age may have been a confounding variable. The possibility of an association between age and audiometric results (hearing threshold) was not addressed.

Electrophysiological Evidence of Neurotoxicity in Children. Electrophysiological studies have provided evidence suggestive of effects on central nervous system function at blood lead levels considerably less than 30 μg/dL, but findings were inconsistent. Linear dose-effect relationships were observed in slow-wave voltage during conditioning in a series of studies (Otto et al. 1981, 1982, 1985) on the same subjects studied by Schroeder et al. (1985). The association was linear throughout the range of blood lead values (6–59 μg/dL). No such relationships were observed in a replicate test, performed on the same subjects studied by Schroeder and Hawk (1987). Brainstem auditory evoked potential (BAEP) latency (Otto et al. 1985; Robinson et al. 1987), pattern-reversal visual evoked potential (PREP) latency and their amplitude were also correlated with blood lead levels (Otto et al. 1985). The specific components affected and the direction of effect varied across studies. These studies did not specify the route and the duration of lead exposure and only accurately measured recent lead exposure; they revealed little about the exposure history of the individual.

Peripheral Nerve Function in Children. Effects of lead on peripheral nerve function have been documented in children. Frank peripheral neuropathy has been observed in children at blood lead levels of 60–136 μg/dL (Erenberg et al. 1974). Of a total of 14 cases of childhood lead neuropathy reviewed by Erenberg et al. (1974), 5 also had sickle cell disease, a finding which the authors suggested might indicate an increased susceptibility to lead neuropathy among children with sickle cell disease. However, effects of race cannot be eliminated. A case study (Seto and Freeman 1964) reported signs of peripheral neuropathy in a child with a blood lead level of 30 μg/dL, but lead lines in the long bones suggested past exposures leading to peak blood lead levels of ≥40–60 μg/dL and probably in excess of 60 μg/dL (EPA 1986a). NCV studies have indicated an inverse correlation between peroneal NCV and blood lead levels over a range of 13–97 μg/dL in children living near a smelter in Kellogg, Idaho (Landrigan et al. 1976). These data were reanalyzed to determine whether a threshold exists for this effect. Three different methods of analysis (segmental, logistic, and quadratic regressions) revealed evidence of a threshold for NCV at blood lead levels of 20–30 μg/dL (Schwartz et al. 1988).

2.2.1.5 Developmental Effects

The best data regarding potential developmental consequences of low-level prenatal exposure to lead are provided by several recent human studies. Because of improved analytical techniques for measuring low lead levels in blood, the availability of large numbers of subjects, and careful consideration of potential confounding factors, these human studies provide useful information on the developmental effects of lead.

Less emphasis has been placed on studies conducted in animals because of the availability of good human data, although a large body of animal data is available and the results are in agreement with those of the human studies. *(See review by Davis et al. [1990] for a comparison of human and animal data in* developmental neurotoxicity.)

In most of these studies, prenatal exposure was generally estimated through maternal and/or cord blood lead concentrations. Exposure of the mothers can be assumed to have been primarily through the oral route, but with contribution from the inhalation route as well. The most relevant studies are discussed below, along with results from a few investigations of different markers for lead exposure.

No reports were found indicating low levels of lead as a cause of major congenital anomalies. Needleman et al. (1984), however, demonstrated an association between blood lead levels and minor congenital anomalies. Using logistic regression modeling techniques and controlling for a number of possible confounders, the authors reported a significant association between cord blood lead levels and the collective occurrence of minor anomalies in 4,354 infants born in Boston. Data were obtained from hospital records. The most common of these anomalies were hemangiomas, lymphangiomas, minor skin anomalies (tags and papillae), and undescended testicles. No individual anomaly was significantly associated with blood lead levels. Major malformations, birth weight, and gestational age were not associated with blood lead levels.

In a cross-sectional study of 236 mothers and their infants in Glasgow, Scotland, Moore et al. (1982) demonstrated reductions in gestational age with increasing cord or maternal blood lead levels. In the 11 cases of premature birth (gestational age <38 weeks), maternal blood lead levels averaged approximately 21 μg/dL, and cord blood lead levels averaged approximately 17 μg/dL at delivery. The overall geometric mean blood lead levels at delivery were 14 μg/dL (maternal) and 12 μg/dL (cord). Statistical analyses showed significant negative coefficients for length of gestation against log-transformed maternal or cord blood levels. Birth weight was not associated with blood lead levels.

An on-going prospective study of the effects on child development following prenatal and postnatal lead exposure in the lead smelter town of Port Pirie, South Australia, and its surrounding areas, provides information on congenital anomalies, length of gestation, birth weight, and stillbirth or miscarriage (McMichael et al. 1986), and on neurobehavioral development (Baghurst et al. 1987, 1992; Vimpani et al. 1985, 1989). Of 831 pregnant women, 774 pregnancies were followed to completion (McMichael et al. 1986). Blood lead levels during pregnancy and at delivery were significantly higher in women who lived in Port Pirie than in those who lived in adjacent towns and rural areas (e.g., at delivery: 11.2 μg/dL in Port Pirie and 7.5 μg/dL in the surrounding areas). No association was found between the blood lead levels and the occurrence of congenital anomalies when pertinent risk factors, such as smoking and alcohol consumption, were controlled for. As was the case with Needleman's study (1984), hospital records were used to detect congenital anomalies. This may have caused a lack of precision and uniformity. Also, the relatively small number of subjects may not have been sufficient for detection of differences in low frequencies of anomalies. Multivariate analysis revealed a significant association between preterm delivery (before the 37th week of pregnancy) and maternal blood lead levels at delivery. The relative risk of preterm delivery increased more than fourfold at blood lead levels of >14 μg/dL compared with a relative risk of 1 at blood lead levels of ≤8 μg/L. The incidence of low birth weight (<2,500 g at gestational age ≥37 weeks) was greater in Port Pirie than in the surrounding areas, but maternal and cord blood lead levels at delivery were somewhat lower in the low-birth-weight pregnancies. Similarly, 22 of the 23 miscarriages and 10 of the 11 stillbirths in this study occurred in the Port Pirie mothers, but the average maternal blood lead level at delivery was significantly lower for stillbirths than for live births.

The results of McMichael et al. (1986) are puzzling because the proportion of Port Pirie pregnancies (delivery maternal blood lead = 10.4 μg/dL) resulting in low-birth weight infants was more than twice that for outside pregnancies (delivery maternal blood lead = 5.5 μg/dL). Yet the maternal and cord blood lead levels were somewhat lower in low birth-weight pregnancies than in pregnancies with birth weights >2,500 g. A similar phenomenon was seen with regard to stillbirths, which occurred primarily in the Port Pirie pregnancies, but which were associated with lower maternal blood lead levels than were live births. Davis and Svendsgaard (1987) suggested that the findings for blood lead versus birth weight or stillbirth in the Port Pirie study suggest an increased transfer of lead from mother to fetus, which is toxic to the fetus. This suggestion is supported by the inverse correlation between placental lead levels and birth weight, head circumference, and placental weight reported by Ward et al. (1987) and the increased levels of lead in the placenta reported by Wibberley et al. (1977) in cases of stillbirth and neonatal death. Alternatively, it has been suggested that such findings may indicate that lead accumulates in the placenta in times of fetal stress (Wibberley et al. 1977).

In a prospective study by Factor-Litvak et al. (1991), prenatal lead exposure versus reproductive outcome (intrauterine growth and preterm delivery) were assessed in pregnant women from two towns in Yugoslavia. Titova Mitrovica is a lead smelter town, while Pristina is an unexposed town 25 miles further south. At mid-pregnancy, 401 and 506 women were recruited from T. Mitrovica and Pristina, respectively, with mean blood lead concentrations of 0.92 and 0.27 μmol/L (19 and 5.6 μg/dL) in the respective group; at time of delivery, these concentrations were 1.13 and 0.33 μmol/L (23.4 and 6.8 μg/dL), respectively. No differences were found between the two areas for either birth weight or length of gestation. In addition, no associations were observed between blood lead concentrations (maternal and cord, at mid-term and time of delivery) and birth weight, length of gestation, or preterm delivery (<37 weeks).

Greene and Ernhart (1991) conducted further analyses of the 132 mother-infant pairs in the Cleveland Prospective Study (see below for more details; Ernhart et al. 1985, 1986, 1987; Wolf et al. 1985). A potential relationship between prenatal lead exposure and neonatal size measures (weight, height and head circumference) and gestational age was investigated. No such relationship was observed.

Exposure to low levels of lead has been shown to interfere with the mental development of children. Preliminary results of blood lead and neurobehavioral testing of 592 children from the Port Pirie study were reported by Baghurst et al. (1987), Vimpani et al. (1985, 1989), and Wigg et al. (1988). In these children, geometric mean blood lead levels increased from approximately 14 μg/dL at 6 months of age to approximately 21 μg/dL at 15 and 24 months. At 24 months, approximately 20% of the children had blood lead levels >30 μg/dL. Neurobehavioral tests--the Bayley MDI and Bayley Psychomotor Development Index (PDI)--were conducted at 24 months. Multiple regression analyses indicated that reduced MDI scores were significantly (p=0.07) associated with higher integrated postnatal blood lead levels and with 6-month blood lead levels, but not with prenatal delivery or cord blood lead levels. Controlling for both maternal IQ and Home Observation for Measurement of the Environment (HOME) scores, the association between 6-month blood leads and 24-month MDI scores remained significant, with a 2-point deficit in MDI for every 10-μg/dL increase in blood lead. A follow-up of this cohort involved blood lead testing at 3 and 4 years of age and neurobehavioral assessment using the McCarthy Scales of Children's Abilities (McMichael et al. 1988). Multiple regression analyses showed that children's scores on these tests were significantly and inversely correlated with log blood lead levels at 6, 24, and 36 months and with the integrated average for birth to 4 years. The estimated decrease in the GCI score was approximately 7.2 points for an increase in integrated average blood lead from 10 to 30 μg/dL. The neurobehavioral development of this cohort, as assessed by the WISC was again studied at 7 years of age (n=494) (Baghurst et al. 1992). Multiple regression analysis adjusting for sex, parents' level of education, maternal age at delivery, parents' smoking status, socioeconomic status, quality of the home environment, maternal IQ, birth weight, birth order, feeding method, duration of breast-feeding, and whether the child's natural parents were living together revealed a statistically significant inverse relationship between IQ and blood lead levels from birth through 7 years of age. This relationship was more evident for blood lead levels at 15 months to 4 years. The IQ was reduced by 4.4–5.3 points for an increase in blood lead levels of 10–30 μg/dL.

In other prospective studies (Bellinger et al. 1984, 1985a, 1985b, 1986a, 1986b, 1987a, 1987b), cord blood lead levels were determined at delivery, for 249 middle-class and upper-middle class Boston children. Blood lead levels and MDI, PDI scores were measured every 6 months thereafter. Infants born at <34 weeks of gestation were excluded from the study. Cord blood lead values were <16 μg/dL for 90% of the subjects, with the highest value being 25 μg/dL. On the basis of cord blood lead levels, the children were divided into low-dose (<3 μg/dL; mean = 1.8 μg/dL), medium-dose (6–7 μg/dL; mean = 6.5 μg/dL), and high-dose (≥10 μg/dL; mean = 14.6 μg/dL) exposure groups. A slight but not significant direct correlation between cord blood lead category and length of gestation was seen. However, analysis within gestational age categories indicated no correlation between cord blood lead category and length of gestation (Bellinger et al. 1984, 1985a). The percentage of infants that were small for their gestational age increased with increasing cord blood lead, although the trend was not statistically significant (Bellinger et al. 1984). Multivariate regression analysis revealed an inverse correlation between cord blood lead levels and MDI scores at 6, 12, 18, and 24 months of age (Bellinger et al. 1985a, 1985b, 1986a, 1986b, 1987a). The high-lead group had an average deficit of 4.8 points on the covariate-adjusted MDI score as compared with the low-lead group. MDI did not correlate with postnatal blood lead levels. No correlations between PDI and cord or postnatal blood lead levels were seen. The findings of earlier studies (Bellinger et al. 1985a, 1985b, 1986a, 1986a, 1987b) were confirmed in more recent studies (Bellinger et al. 1989a, 1989b) and suggest that the younger the infants are, the more vulnerable they are to lead-induced developmental toxicity. Moreover, the decline in MDI scores varied with the child's age at exposure, the level of exposure, and socioeconomic status (Bellinger et al. 1989b). Infants in lower socioeconomic groups showed deficits at lower levels of prenatal exposure (mean blood lead levels = 6–7 μg/dL) than children in higher socioeconomic groups. The early postnatal blood lead levels (range = 10–25 μg/dL) were also associated with lower MDI scores, but only among children in lower socioeconomic groups. Additional follow-up showed deficits in GCI scores of these children at approximately 5 years of age, which correlated significantly with earlier blood lead levels (at 24 months of age) but not with prenatal blood lead levels (Bellinger et al. 1991). These results suggest that prenatal blood lead levels are a better predictor of cognitive development in infants than in 4–5-year-old children and that early developmental deficits associated with elevated blood lead may not persist until 4–5 years of age, especially in socioeconomically advantaged families.

Interim results of an investigation of 185 subjects and later results from the complete follow-up sample of 305 subjects in a prospective study of inner-city children born in Cincinnati, Ohio, were reported by Dietrich et al. (1986, 1987a, 1987b). Maternal blood lead levels were measured at the first prenatal visit; cord blood was measured at delivery; infant blood lead levels were measured at 10 days and at 3 months of age; and neurobehavioral tests were performed at 3 and 6 months of age. Mean blood lead levels were as follows: prenatal (maternal)--8.0 μg/dL (range = 1–27 μg/dL); umbilical cord--6.3 μg/dL (range = 1–28 μg/dL); 10-day-old and 3-month-old infants--4.6 and 5.9 μg/dL (range = 1–22 μg/dL for each). Multiple regression analyses, with perinatal health factors such as birth weight and gestational age treated as confounders, showed inverse correlations between prenatal or cord blood lead levels and performance on the MDI at 3 months, and between prenatal or 10-day neonatal blood lead levels and performance on the MDI at 6 months. No significant correlation of blood lead level with PDI was seen. Male infants and low socioeconomic status infants appeared to be more sensitive to the effect on the MDI. Multiple regression analyses for male or low socioeconomic status infants showed covariate-adjusted decrements of 0.84 or 0.73 MDI points per µg/dL of prenatal or 10-day neonatal blood lead, respectively (i.e., an approximate 8-point deficit for a 10-µg/dL increase in blood lead) (Dietrich et al. 1987a).

Further analyses by structural equation modeling in the study by Dietrich et al. (1987a) showed that the effect of prenatal lead exposure on MDI was in part mediated through its effects on birth weight and gestational age. Higher prenatal blood lead levels were associated with reduced birth weight and reduced gestational age, which were each significantly associated with reduced MDI scores (Dietrich et al. 1987a). Separate, preliminary analyses of the data from the Cincinnati study by Bornschein et al. (1989) indicated that for each natural log unit increase in blood lead, the decrease in birth weight averaged 114 g, but ranged from 58 to 601 g depending on the age of the mother. The authors reported that the threshold for this effect could be approximately 12-13 µg/dL blood lead. In addition, a decrease in birth length of 2.5 centimeters per natural log unit of maternal blood lead was seen, but only in white infants. In a later report, the blood lead levels during prenatal (maternal blood level = 8.2 µg/dL, range = 1-27 µg/dL) and neonatal (4.8 µg/dL, range = 1-23 µg/dL) periods were found to be inversely related to a complex of sensorimotor developmental indices at 6 and 12 months of age. The prenatal maternal blood level was also related to lower birth weight, which in turn was related to poorer sensorimotor performance in infants during the 1st year of age (Dietrich et al. 1989).

A follow-up of the 260 infants from the Cincinnati cohort revealed that postnatal growth rates, measured as covariate-adjusted increases in stature from 3 to 15 months of age, were inversely correlated with postnatal increases in blood lead levels from 3 to 15 months of age (Shukla et al. 1987, 1989). This relationship was significant only for infants with relatively higher prenatal lead exposures (i.e., those whose mothers had prenatal blood lead levels of ≥7.7 µg/dL).

Some neurobehavioral effects (ability to self-quiet and to be consoled) appeared to be associated with a rise in maternal blood lead levels from 36 weeks gestation to birth (Rothenberg et al. 1989a). Absolute blood lead levels did not appear to be associated with effects. These results were obtained on 42 mother-infant pairs selected in the Mexico City pilot study. Blood samples were obtained at 36 weeks gestation from the mother. At birth, cord blood samples and maternal samples were obtained. The Brazelton Neonatal Behavioral Assessment Scale (NBAS) was administered by psychologists certified in the use of this instrument. The principal shortcoming of this study is the small sample size (42-50 mother-baby pairs, depending on the end point measured). Large numbers of statistical analyses were performed, increasing the likelihood that some significant associations would occur by chance. Cord blood levels of lead were measured and not actual fetal blood lead levels.

In a prospective study of mothers and infants in Cleveland, Ohio (Ernhart et al. 1985, 1986, 1987; Wolf et al. 1985), mean blood lead levels at the time of delivery were 6.5 µg/dL (range = 2.7-11.8 µg/dL) for 185 maternal samples and 5.8 µg/dL (range = 2.6-14.7 µg/dL) for 162 cord samples. There were 132 mother-infant pairs of data. The infants were evaluated for anomalies using a systematic, detailed protocol and for neurobehavioral effects using the NBAS and part of the Graham-Rosenblith Behavioral Examination for Newborns (G-R), including a Neurological Soft Signs scale. Hierarchical regression analysis was performed. No evidence of an association between blood lead levels and morphological anomalies was found. This relatively small number of subjects, however, may not have been sufficient for the detection of differences in low frequencies of anomalies. Using the complete set of data, abnormal reflexes and neurological soft signs scales were significantly related to cord blood lead levels and the muscle tonicity scale was significantly related to maternal blood lead level. Using data from the mother-infant pairs, the only significant association found was between the Neurological Soft Signs score and cord blood lead levels which averaged 5.8 μg/dL and ranged up to only 14.7 μg/dL; no association with maternal blood lead levels was seen (Ernhart et al. 1985, 1986). A brief, preliminary report on later outcomes from this study reported a significant association between the Neurological Soft Signs measure and the MDI scores at 12 months (Wolf et al. 1985). Hence, it is possible to infer an indirect effect of cord blood lead on MDI (Davis and Svendsgaard 1987; EPA 1986a), although Ernhart et al. (1985, 1986) did not reach such a conclusion. The effects noted by these investigators were significantly related to cord blood lead levels that averaged 5.8 μg/dL and ranged upward to only 14.7 μg/dL.

A later analysis (Ernhart et al. 1987) related blood lead levels obtained at delivery (maternal and cord blood) and at 6 months, 2 years, and 3 years of age to developmental tests (MDI, PDI, Kent Infant Development Scale [KID], and Stanford-Binet IQ) administered at 6 months, 1 year, 2 years, and 3 years of age as appropriate. After controlling for covariates and confounding risk factors, the only significant associations of blood lead with concurrent or later development were an inverse association between maternal (but not cord) blood lead and MDI, PDI, and KID at 6 months, and a positive association between 6-month blood lead and 6-month KID. The investigators concluded that, taken as a whole, the results of the 21 analyses of correlation between blood lead and developmental test scores were "reasonably consistent with what might be expected on the basis of sampling variability," that any association of blood lead level with measures of development was likely to be due to the dependence of both blood lead and development on the caretaking environment, and that if low-level lead exposure has an effect on development the effect is quite small. Ernhart et al. (1987) also analyzed for reverse causality (i.e., whether developmental deficit or psychomotor superiority in infants at 6 months of age contributes to increases in subsequent blood lead levels). No significant correlations were observed when covariates were controlled.

The predictive value of different markers of lead exposure for neurobehavioral performance (WISC verbal, performance, and full-scale IQs; Wiener [Vienna] reaction performance tests; Cued Reaction Time) was investigated by Winneke et al. (1985a, 1985b). This investigation involved the follow-up, at 6–7 years of age, of 114 children from an original study population of 383 children born in Nordenham, Germany. At delivery, the mean maternal blood lead level was 9.3 μg/dL (range = 4–31 μg/dL), and the mean cord blood lead level was 8.2 μg/dL (range = 4–30 μg/dL); most of the blood levels were ≤15 μg/dL. Cord and maternal blood lead levels were highly correlated. Stepwise multiple regression analyses indicated that maternal blood lead levels at delivery accounted for nearly as much of the variance in neurobehavioral test scores at 6–7 years as did contemporary blood lead levels in the children. With either exposure marker, significance was seen only in increased errors on the Wiener Reaction Performance tests.

Bonithon-Kopp et al. (1986b) investigated another potential marker for lead exposure. Maternal and infant hair lead levels, determined from hair samples taken at birth, were found to be correlated inversely with results on neurobehavioral tests (McCarthy Scales of Children's Abilities) when the children were tested at 6 years of age. Other studies have also reported associations between hair lead levels and behavioral or cognitive test scores, but measures of lead in hair may not accurately reflect internal body burden of lead, and such data cannot be used to evaluate internal dose-response relationships (EPA 1986a).

A few studies have reported associations between prenatal lead exposure and changes in heme metabolism. In a study of 294 mother-infant pairs, Haas et al. (1972) reported mean blood lead levels of 16.98 μg/dL for mothers and 14.98 μg/dL for newborns. Infant blood lead levels and ALA-U were positively correlated. The authors, however, did not report the levels of ALA-secretion in infants and mothers with no lead exposure. In pregnant urban women (Kuhnert et al. 1977), cord erythrocyte lead levels ranged from 16 to 67 μg/dL of cells (mean: 32.9 μg/dL) and were inversely correlated with ALAD activity, as were maternal erythrocyte lead levels. In a study of 500 mothers at delivery, Lauwerys et al. (1978) reported negative correlations between blood lead levels and ALAD activity in both mothers and their infants (cord blood). No correlation between blood lead level and erythrocyte protoporphyrin was seen. Blood lead levels averaged 10.2 μg/dL with a range of 3.1–31 μg/dL in the mothers and 8.4 μg/dL with a range of 2.7–27.3 μg/dL in the infants. Taken together, the results of these studies indicate that ALAD activity may be a more sensitive indicator of lead effects on fetal heme synthesis than erythrocyte protoporphyrin or ALA-U levels (EPA 1986a). In contrast to the findings of Lauwerys et al. (1978), the measurement of maternal and umbilical cord lead levels and FEP levels for 95 mother-infant pairs from Toronto showed a significant inverse correlation. Most infants had cord blood lead levels below 7 μg/dL; the cord blood FEP levels were higher than the maternal levels (Koren et al. 1990). The higher FEP levels apparently reflect immature heme synthesis. These results clearly indicate a need to design a study to identify a higher risk of lead exposure among babies of mothers from lead-polluted areas.

Developmental effects that have been observed in humans following exposure to low levels of lead include reduced birth weight, reduced gestational age and neurobehavioral deficits or delays. No evidence of an association with major congenital malformations has been found, although one study reported an association between cord blood lead levels and the collective occurrence of minor anomalies. The evidence for an association between blood lead levels and reduced birth weight and gestational age is inconsistent. The weight of evidence indicates that there may not be a direct association. There is a predominance of negative results with the most recent (and presumably best designed) studies showing no such association. The evidence in support of neurobehavioral deficits or delays is more consistent with most of the studies indicating that there is an association between lead exposure at low levels and developmental neurobehavioral effects.

2.2.1.6 Reproductive Effects

A large body of literature clearly indicates that high levels of lead cause adverse effects on both male and female human reproductive functions. Women in particular, who are exposed during pregnancy, have experienced miscarriages and stillbirths. Although the mechanisms underlying these effects are unknown at this time, many factors could contribute to such results. These factors range from indirect effects of lead on maternal nutrition or hormonal status before and during pregnancy to more direct gametogenic effects that could affect parental fertility in both sexes. The long-known association of lead exposure with a high likelihood of spontaneous abortion has led to the exclusion of women from high-exposure occupations (EPA 1986a), although these earlier studies suffer from methodological inadequacies and the lack of dose-effect information. Human data have largely been derived from studies involving relatively small numbers of subjects and therefore do not allow for discriminating statistical analysis. Reproductive effects of exposure to chronic low levels of lead are less known. The results of two recent studies in females with blood lead levels of 10 μg//dL indicate no effect on the rate of spontaneous abortions. One study in males indicate that at moderate blood lead levels (40–50 μg/dL) sperm production may be affected.

Selected studies are discussed below and include reports on occupational exposure to lead for females and males followed by environmental (low levels) exposure to lead in females and males.

An increased frequency of spontaneous abortion was reported in women living closest to a lead smelter (Nordstrom et al. 1979). Moreover, the female workers at the smelter had an increased frequency of spontaneous miscarriage when employed at the smelter during pregnancy, or when employed at the smelter prior to pregnancy and still living near the smelter. Women who worked in more highly contaminated areas of the smelter were more likely to have aborted than were other women. These studies were confounded by the presence of other toxic agents and by the lack of matching for socioeconomic status, which could also bear on the women's health (EPA 1986a).

Pregnancies were evaluated in the center (high environmental lead exposure; mean maternal mid-pregnancy blood lead level was 10.6 μg/dL; n=645) and in the surrounding areas (low environmental lead exposure; mean maternal mid-pregnancy blood lead level was 7.6 μg/dL; n=185) of Port Pirie, South Australia (a lead smelter town). While no association was found between blood lead levels and spontaneous abortions, 22 of 23 miscarriages and 10 of 11 stillbirths occurred in the Port Pirie residents, with only 1 miscarriage and 1 stillbirth occurring in residents outside Port Pirie (Baghurst et al. 1987; McMichael et al. 1986;). Maternal blood lead levels were lower in the cases of stillbirth than in the cases of live birth, but fetal and placental levels in this and another study (Wibberley et al. 1977) were higher than in cases of normal birth. Davis and Svendsgaard (1987) suggested that these findings may be due to a transfer of lead from mother to fetus, which is toxic to the fetus. This study is discussed more fully in the section on developmental toxicity (Section 2.2.1.5) because the study focuses primarily on the effects of prenatal exposure to low levels of lead on fetal and early childhood development.

The rates of spontaneous abortions were compared in a prospective study (Murphy et al. 1990) in females living close to a lead smelter (n=304; mid-pregnancy mean blood lead concentration of 15.9 μg/dL) and females living 25 miles away (n=335; mid-pregnancy mean blood lead concentration of 5.2 μg/dL). Women were recruited at mid-pregnancy and their past reproductive history (first pregnancy; spontaneous abortion=fetal loss prior to 7th month; stillbirth=fetal loss from 7th month) was examined. The results indicated no difference between the towns regarding the rate of spontaneous abortions. The rates were 16.4% and 14.0% for the lead smelter town and the unexposed town, respectively.

Hu (1991) examined the long-term consequences among survivors of childhood plumbism. Survivors consisted of children admitted to the Boston Children's Hospital from 1930 to 1944 for childhood plumbism. Matched controls (age, sex, and neighborhood) were enlisted through the use of town books. All participants were asked to respond to a self-administered questionnaire. Information on all pregnancies engendered (men) or carried (women); outcome; and intellectual development of resulting children were given. Among the matched females, the rate of spontaneous abortion or stillbirths among pregnancies was higher than for the controls (relative risk = 1.60; 95% confidence interval = 0.6-4.0). In addition, the offspring from a matched female plumbism subject was more likely to experience learning disabilities (relative risk = 3.0; 95% confidence interval = 0.9-10.2). Although this study included only a small number of plumbism survivors, the results indicate that women significantly exposed during childhood may be at risk even later in life for adverse reproductive outcomes.

Lead-induced effects on male reproductive functions have been reported in humans (Assennato et al. 1987; Chowdhury et al. 1986; Lancranjan et al. 1975; Wildt et al. 1983). A group of 150 workmen with long-term lead exposure were categorized by clinical and toxicological data into four groups: lead-poisoned (mean blood lead level = 74.5 μg/dL), and moderately (mean = 52.8 μg/dL), slightly (mean = 41 μg/dL), or physiologically (mean = 23 μg/dL) exposed to lead (Lancranjan et al. 1975). The lead-poisoned group and the moderately exposed group had decreases in fertility, as measured by asthenospermia, hypospermia, and teratospermia. The effect of lead was thought to be directly on the testes because tests for changes in gonadotropin secretion were negative. Secretion of androgens by the testes was not affected.

Another study compared two groups of men in a Swedish battery factory (Wildt et al. 1983). The men exposed to high levels of lead had blood lead levels of ≥50 μg/dL at least once prior to the study and had mean blood lead levels of 46.1 and 44.6 μg/dL (range = 25-75 μg/dL) during fall and spring test periods.

The controls (exposed only to low environmental levels of lead) had blood lead levels that seldom exceeded 30 μg/dL, and had mean blood lead levels of 21.1 and 21.5 μg/dL (range = 8–39 μg/dL) during fall and spring test periods. The high-lead group tended to exhibit decreased prostate/seminal vesicle function as measured by seminal plasma constituents, low semen volumes, and lower functional maturity of sperm (as measured by swelling of the sperm heads in detergent [sodium dodecyl sulfate] solution). Weaknesses of the study include the relatively high blood lead levels of the controls and current or past urogenital tract infections in some of the controls and in none of the high-lead men. Moreover, the small sample size did not allow a reliable statistical analysis.

Chowdhury et al. (1986) reported that occupational exposure of 10 men to lead caused a significant decrease in sperm count and motility and an increased percentage of abnormal spermatozoa. The average blood lead concentration in the lead-exposed group was higher (42.5 μg/dL) compared to controls (14.8 μg/dL). Assennato et al. (1987) reported decreased sperm production in 39 battery factory workers with high blood lead levels ranging from 50 to 61 μg/dL when compared to 39 nonexposed workers. These studies, however, were limited by the small sample size.

In a cohort study, Coste et al. (1991) conducted a person-year analyses and reported no effects on fertility (defined as the number of live births to a couple) among men exposed to lead in a French battery factory. Exposed workers (229) were categorized into groups with blood lead levels of <40 μg/dL, 40–60 μg/dL, and >60 μg/dL. Nonexposed workers (125) did not have their blood lead levels recorded. The results of this study are not in concordance with studies that have evaluated similar end points. This may be explained by uncontrolled confounding factors relating to the nonexposed women and limited exposure information.

Studies of lead workers with higher blood lead levels (≥66 μg/dL) indicate that lead acts directly on the testes to cause severe depression of sperm count and peritubular testicular fibrosis, and also produces reduced testosterone synthesis or disrupts regulation of luteinizing hormone (LH) secretion at the hypothalamic-pituitary level (Braunstein et al. 1978; Cullen et al. 1984; Rodamilans et al. 1988). Although these studies had limitations such as concomitant exposure of workers to other chemicals, lack of matched control group, small sample size, and in some cases a possibility of observed effects being precipitated by the EDTA chelation (as in Braunstein et al. 1978), taken together they provide evidence for lead-induced endocrine disturbances and reproductive dysfunction in male workers.

2.2.1.7 Genotoxic Effects

Results of assays made following in vivo exposure from occupational sources are contradictory, but do suggest that lead may have an effect on chromosomes. Increased frequency of sister chromatid exchange was not observed in one study of occupationally exposed adults with blood lead levels of 48.7 μg/dL (Maki-Paakkanen et al. 1981) or in environmentally exposed children with blood lead levels of 30–63 μg/dL (Dalpra et al. 1983). A slight positive correlation between sister chromatid exchange with increasing duration of exposure has been reported in lead-exposed workers (Grandjean et al. 1983). This observation was independent of blood lead level. Similar slight increases of sister chromatid exchanges in lead-exposed workers that may have been confounded by age effects were reported in a study that used too few controls to show conclusive results (Leal-Garza et al. 1986). Increased frequencies of chromosomal aberrations (primarily chromatid-type) were seen in 21 battery factory workers; these elevations were positively correlated with blood lead levels, and showed a marked increase when blood lead levels reached 50 μg/dL. Sister chromatid exchanges were also significantly elevated in these workers when blood lead levels reached 80 μg/dL (Huang et al. 1988b). This study examined a fairly small number of workers, but appropriate selection criteria were used in order to minimize the effects of other potential genotoxic factors, such as smoking, drinking, viral diseases, exposure to medical X-rays, chelation agents, or use of medications with known clastogenic effects. A common problem in these occupational studies is concurrent exposure to many other agents in the occupational environment.

Occupational exposure to lead is associated with increased mitotic activity in peripheral lymphocytes, increased rate of abnormal mitosis (Forni et al. 1976; Sarto et al. 1978; Schwanitz et al. 1970), and increased incidence of chromosomal aberrations (Al-Hakkak et al. 1986; Forni et al. 1976, 1980; Nordenson et al. 1978; Schwanitz et al. 1970) at blood lead levels ranging from 22 to 89 μg/dL. While a positive correlation between blood lead levels and the frequency of chromosomal aberrations has been reported (Nordenson et al. 1978), most of the available data on occupationally exposed workers show no increase in the frequency of chromosomal aberrations when blood lead levels ranged from 38 to 120 μg/dL (Bauchinger et al. 1977; Maki-Paakkanen et al. 1981; O'Riordan and Evans 1974; Schmid et al. 1972; Schwanitz et al. 1975) or in environmentally exposed children with blood lead levels of 12–33 μg/dL (Bauchinger et al. 1977).

Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

The information available that has examined the association of occupational exposure to lead with increased cancer risk is generally limited in its usefulness because the actual compound(s) of lead, the route(s) of exposure, and level(s) of lead to which the workers were exposed were not reported. Furthermore, potential for exposure to other chemicals including arsenic occurred, particularly in lead smelters, and smoking was a possible confounder (Cooper 1976; IARC 1987). These studies, therefore, are not sufficient to determine the carcinogenicity of lead in humans, and the following discussion is restricted to the most comprehensive of these studies.

The most extensive was a series of reports of a large number of workers at 6 domestic lead production plants (smelters and recycling plants) and 10 battery plants (Cooper 1976; Cooper and Gaffey 1975). Increased incidences of total malignant neoplasms were observed for both categories of lead workers, but the increase was statistically significant only for lead production workers. The increase in total malignancies appeared to be due to small, statistically nonsignificant increases in digestive and respiratory tract tumors (evident in both the lead production and battery workers) and urinary tract tumors (in production workers). In a statistical reanalysis of the Cooper and Gaffey (1975) data, Kang et al. (1980) determined that the incidence of total malignant neoplasms, cancers of the digestive tract, and cancers of the respiratory tract were statistically elevated in both lead production workers and battery workers.

In a follow-up to the original study, Cooper (1981) reported that lead had no cancer-inducing properties, although standard mortality ratios (SMRs) of 125–149% for total malignant neoplasms, 172% for respiratory cancer, and 229% for cancers of other sites were reported in battery workers. In a recent evaluation of a more select subset from the original study, Cooper et al. (1985) reported increased SMRs for total malignancies in both groups of workers (statistically significant only in the battery workers) attributed to digestive and respiratory cancers. These small excesses of cancer deaths could not be correlated with onset, duration, or level of exposure. In addition, no adjustments could be made for other concomitant industrial exposures or for smoking. The attributable risk of smoking could easily explain the small increase in respiratory cancer in an industrial cohort that contained an excess of heavy smokers. Also, a marginally significant increase in digestive tract cancer in acid-lead battery workers was observed during the early years of lead exposure (when lead levels were presumably higher than in later years) (Fanning 1988; Malcolm and Barnett 1982).

In a retrospective cohort mortality study of primary lead smelter workers, an SMR of 204% for mortality from renal cancer was calculated (Selevan et al. 1985). Although the results were not statistically significant because of small numbers, the study is of interest because animal studies associate lead exposure with kidney cancer (see Section 2.2.2.8). In addition, two cases of renal cancer have been reported in occupationally exposed men who had symptoms of lead poisoning and high blood lead levels (Baker et al. 1980; Lilis 1981). In one case, the tumor was reported to contain a high level of lead and to have histopathological characteristics similar to those of kidney tumors induced by lead in animals (Baker et al. 1980).

In a study of cancer incidence in workers exposed to tetraethyl lead, a statistically significant association was found between exposure to this compound and rectal cancer (odds ratio = 3.7; 90% confidence limits of 1.3–10.2) (Fayerweather et al. 1991). The odds ratio increased four times at the high-to-very high cumulative exposure level, demonstrating a dose-response relationship. When a 10-year latency was assumed, the association became even more pronounced. No increases in the incidence of cancer at other sites (i.e., brain, kidney, lung, spleen, and bone) were observed in the exposed workers. Despite the strength of the association and the appearance of a dose-response relationship for the effect, the authors of this study caution against assigning any causal relationship to these findings. They explain that the increase in rectal cancer observed in this study may be explained by other causal mechanisms or non-causal mechanisms (such as statistical and methodological bias or chance).

2.2.2 Inhalation Exposure

2.2.2.1 Death

Deaths associated with occupational exposure to inorganic lead (which is predominantly by the inhalation route of exposure) are discussed in Section 2.2.1.1. No studies were located regarding death in animals after inhalation exposure to inorganic lead.

2.2.2.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, musculoskeletal, or dermal/ocular effects in humans or animals after inhalation exposure to inorganic lead.

Respiratory Effects. No studies were located regarding respiratory effects in humans after inhalation exposure to inorganic lead. See Section 2.2.1.2 for a discussion of the respiratory effects of lead in humans after multi-route exposure.

Lung weights in mice continuously exposed to lead nitrate at a concentration of 1.6 mg lead/m^3 for 28 days were slightly but significantly elevated. The lungs from these mice appeared hemorrhagic at necropsy. These effects were most likely due to pulmonary edema resulting from an irritative response to the inhalation of lead aerosol for 28 days (Hillam and Ozkan 1986). Increased lung weight and hemorrhage were not observed in the lungs of mice similarly exposed for 14 days, indicating that the effects observed in mice exposed for 28 days were exposure duration dependent (Hillam and Ozkan 1986). This LOAEL is presented in Table 2-2 and plotted in Figure 2-1.

TABLE 2-2. Levels of Significant Exposure to Lead - Inhalation

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg/m^3)	LOAEL (effect) Less serious (mg/m^3)	LOAEL (effect) Serious (mg/m^3)	Reference	Form[b]
ACUTE EXPOSURE								
Immunological								
1	Mouse	14 d 7d/wk 24hr/d			1.6 (decreased spleen and thymus weight; decreased splenic and thoracic lymph node antibody forming cells; decreased total leukocyte count)		Hillam and Ozkan 1986	$Pb(NO_3)_2$
INTERMEDIATE EXPOSURE								
Systemic								
2	Human	18 wk 23hr/d	Hemato		0.011 (47% decrease in ALAD activity)		Griffin et al. 1975b	
3	Rat	3 wk 7d/wk 24hr/d	Hemato		1 (decreased ALAD activity)		Prigge and Greve 1977	
4	Mouse	28 d 7d/wk 24hr/d	Resp		1.6 (increased lung weight; hemorrhagic)		Hillam and Ozkan 1986	$Pb(NO_3)_2$
			Hepatic		1.6 (increased liver weight)			
			Renal	1.6				
			Other	1.6				

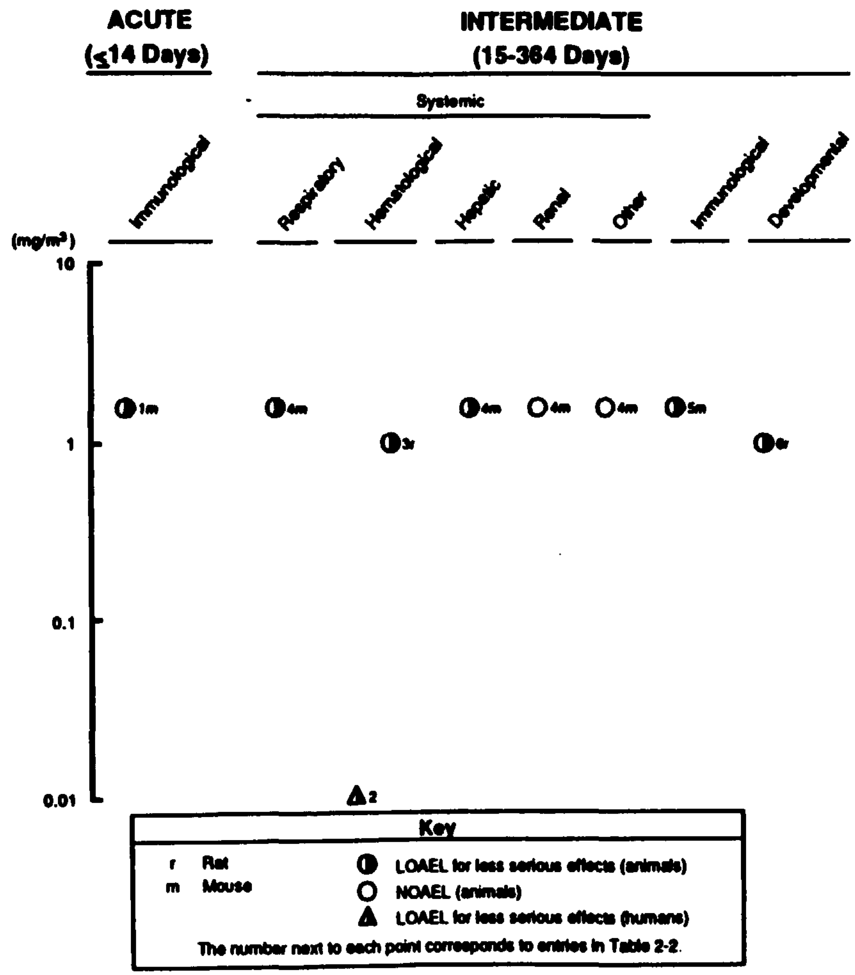
TABLE 2-2 (Continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg/m^3)	LOAEL (effect) Less serious (mg/m^3)	LOAEL (effect) Serious (mg/m^3)	Reference	Form[b]
Immunological								
5	Mouse	28 d 24hr/d 7d/wk			1.6 (decreased spleen and thymus weight, decreased leukocyte count, decrease in antibody titer following i.p. immunization; decreased splenic antibody forming cells)		Hillam and Ozkan 1986	$Pb(NO_3)_2$
Developmental								
6	Rat	3 wk 7d/wk 24hr/d Gd1-21			1 (decreased ALAD in fetus)		Prigge and Greve 1977	

[a]The number corresponds to entries in Figure 2-2.
[b]If not specified, not known

ALAD = delta-aminolevulinic acid dehydratase; d = day(s); Gd = gestation day(s); Hemato = hematological; hr = hour(s); i.p. = intraperitoneal; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; $Pb(NO_3)_2$ = lead nitrate; Resp = respiratory; wk = week(s)

FIGURE 2-1. Levels of Significant Exposure to Lead - Inhalation



Hematological Effects. As discussed in Section 2.2.1.2, lead has long been known to affect heme biosynthesis by affecting the activities of several enzymes of the heme biosynthetic pathway. Lead has long been known to have profound effects on heme biosynthesis. Lead inhibits the activity of certain enzymes involved in heme biosynthesis, namely, ALAD, ferrochelatase, and coproporphyrinogen oxidase. The mechanisms for these effects are discussed in detail in Section 2.4. As a consequence of these changes, the activity of the rate limiting enzyme of the pathway, ALAS, is subsequently increased. The end results of these changes in enzyme activities are increased urinary porphyrins, coproporphyrin, and ALA; increased blood levels of ALA; and increased EP, FEP, and ZPP (EPA 1986a).

In one study, adult male volunteers were exposed to particulate lead in air at 0.003 or 0.01 mg lead/m^3 for 23 hours a day for 3–4 months. Mean blood lead levels increased from 20 μg/dL (preexposure) to 27 μg/dL at the 0.003 mg/m^3 exposure level and from 20 μg/dL (preexposure) to 37 μg/dL at the 0.01-mg/m^3 exposure level. ALAD decreased to approximately 80% of preexposure values in the 0.003-mg/m^3 group after 5 weeks of exposure and to approximately 53% of preexposure values in the 0.01-mg/m^3 group after 4 weeks of exposure (Griffin et al. 1975b). These results are presented in Table 2-2 and plotted in Figure 2-1.

Hepatic Effects. A significant increase in liver weight was observed in mice continuously exposed to 1.6 mg/m^3 lead nitrate for 14 or 28 days as compared to air-exposed control animals (Hillam and Ozkan 1986). Although the authors suggest that these results indicate that inhalation exposure to lead may be toxic to the liver, no functional (i.e., serum enzyme) or histopathological studies were conducted. Therefore, the toxicological significance of this increase in liver weight is not known.

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to inorganic lead. See Section 2.2.1.2 for a discussion of the other systemic effects of lead in humans after multi-route exposure.

No increase in kidney weight was noted in mice continuously exposed to lead nitrate for 28 days (Hillam and Ozkan 1986). No other studies were located regarding renal effects in animals after inhalation exposure to inorganic lead.

Other Systemic Effects. No studies were located regarding other systemic effects in humans after inhalation exposure to inorganic lead. See Section 2.2.1.2 for a discussion of the other systemic effects of lead in humans after multi-route exposure.

No effects on body weight were noted in mice continuously exposed to lead nitrate for 28 days (Hillam and Ozkan 1986). No other studies were located regarding other systemic effects in animals after inhalation exposure to inorganic lead.

2.2.2.3 Immunological Effects

The effects of intermediate-duration inhalation lead exposure on local and systemic immune function following intratracheal, intraperitoneal, or intravenous immunization were studied in mice continuously exposed to lead nitrate for 14 or 28 days (Hillam and Ozkan 1986). Several parameters of local and systemic immune function were measured in the immunized, lead-exposed mice. Lead content was significantly higher in the liver, spleen, thymus, lung, and kidney as compared to the control group in both the 14-day and 28-day exposure groups, but the effect was more pronounced in the 28-day exposure group. Both splenic and thymic weights were significantly decreased in all of the lead-exposed animals as compared to the controls. Decreases in leukocyte counts, circulating antibodies, and antibody forming cells were noted in different lead exposed groups. Based on these results, it would appear that lead induces immunosuppression. Furthermore, since only the thoracic lymph node response was suppressed after intravenous immunization, it would appear that inhaled lead does not cause systemic immunosuppression. These results also demonstrate that inhaled lead accumulates in the body, since higher tissue levels were observed following 28 days of exposure as compared to 14 days of exposure, and the immunosuppressive effects were more pronounced in the mice exposed for 28 days as compared to those exposed for 14 days. The LOAEL from this experiment is presented in Table 2-2 and plotted in Figure 2-1.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals after inhalation exposure to inorganic lead. See Section 2.2.1.4 for a discussion of the neurological effects of lead in humans after multi-route exposure.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to inorganic lead. See Section 2.2.1.5 for a discussion of the developmental effects of lead in humans after multi-route exposure.

The data from the only available animal study (Prigge and Greve 1977) indicate that lead is not teratogenic. However, it impaired heme synthesis in both rat dams and fetuses. In this study, dams were exposed to various levels of lead throughout gestation (days 1-21). Maternal and fetal ALAD were inhibited at all exposure levels in a dose-related manner and fetal, but not maternal, hematocrit and body weight were decreased at the 10-mg/m^3 lead level. These results suggest that the fetuses were more sensitive to lead-induced toxicity than were the dams. The LOAEL from this study is presented in Table 2-2 and plotted in Figure 2-1.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after inhalation exposure to inorganic lead. See Sections 2.2.1.6 and 2.2.1.7 for a discussion of these effects in humans after multi-route exposure to inorganic lead.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to inorganic lead. See Sections 2.2.1.6 and 2.2.1.7 for a discussion of these effects in humans after multi-route exposure to inorganic lead.

Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans or animals after inhalation exposure to inorganic lead. See Section 2.2.1.8 for a discussion of cancer in humans following multi-route exposure to inorganic lead.

2.2.3 Oral Exposure

2.2.3.1 Death

Oral LD_{50} values for lead or its inorganic or organic salts were not found in the available literature. LD_{LO} values for a number of lead compounds have been estimated (Sax 1984, see Table 2-3). An LD_{LO} is defined as the lowest dose of a substance given over any given period of time in one or more divided portions reported to have caused death (Sax 1984). Furthermore, unlike LD_{50}s, these values are not derived statistically, and comparisons between compounds and species are difficult.

Increased mortality was observed in a 2-year feeding study in rats (Azar et al. 1973). However, the increased mortality did not occur in a dose-related manner. Statistical analyses were not provided. The authors stated that the reason for these discrepant results was not known. The apparent lack of a dose-response relationship in either sex precludes meaningful conclusions regarding effect levels for mortality in this study.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory effects in humans or animals following oral exposure to inorganic lead. See Section 2.2.1.2 for a discussion of the respiratory effects of lead in humans after multi-route exposure.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following oral exposure to inorganic lead. See Section 2.2.1.2 for a discussion of the cardiovascular of lead in humans after multi-route exposure.

There is a large database that describes cardiovascular (primarily hypertensive) effects in laboratory animals resulting from exposure to lead. In the earlier studies, relatively high doses of lead were administered (i.e., 70 mg/day), and it is difficult to determine whether the hypertension observed in the treated animals was due to a direct effect of lead or was secondary to lead-induced renal damage (Victery 1988). Furthermore, increases in blood pressure were not always observed in these studies, and sometimes decreases in blood pressure were observed, and blood lead levels were not always quantified, making comparisons across studies difficult because of considerable experimental design differences (Victery 1988). The more recent chronic-duration exposure studies at doses that are otherwise nontoxic clearly indicate that lead ingestion is associated with an elevation in blood pressure that is sustained over a considerable portion of the animal's life span. For example, male rats given lead acetate at 50 ppm lead in the drinking water for 160 days had markedly increased blood pressure of 182/138 (systolic/diastolic) as compared with 128/98 in controls (Iannaccone et al. 1981) when anesthetized with pentobarbital. The mean blood lead level of the treated group was 38.4 μg/dL. Male rats administered lead acetate at 5 or 25 ppm lead in the drinking water for 5 months beginning in utero (blood lead levels of 5.6 and 18.2 μg/dL, respectively) did not develop hypertension, although plasma renin activity was increased at 25 ppm (Victery et al. 1982b). However, exposure of male rats to 100 ppm lead as lead acetate in drinking water for 6 months beginning in utero resulted in a 17-mmHg increase in blood pressure after 3.5 months of exposure as compared to the control animals when unanesthetized. No change in blood pressure was observed in rats administered 500 ppm lead. It should be noted that kidney effects (e.g., increased kidney weight and intranuclear inclusion bodies) were observed at 100 ppm and/or 500 ppm (Victery et al. 1982a).

TABLE 2-3. Oral LD_{LO} Values for Lead Compounds[a]

Compound	Species	LD_{LO} (mg/kg)[b]	LD_{LO} (mg lead/kg)
Lead acetate	Dog	300	191
Lead chloride	Guinea pig	2,000	1,490
Lead nitrate	Guinea pig	500	313
Lead oxide	Dog	1,400	1,300
Lead sulfate	Dog	2,000	1,366
	Guinea pig	30,000	20,500

[a]Source: Sax 1984
[b]Based on the weight of individual compounds

LD_{LO} = lowest dose expected to cause death

An increase in systolic blood pressure was observed in rats at a very low exposure level (1 ppm lead in the drinking water for 159 days, but the dietary and drinking water content of essential and nonessential metals was abnormally low, and the low-contamination quarters in which the rats were housed also limited their exposure to essential and nonessential metals (Perry and Erlanger 1978). These conditions, which result in greater absorption of lead and effects at lower lead intakes than when the diet is less restricted and the living quarters less isolated, may not be relevant to human exposure. Increases in blood pressure at low exposure levels have been demonstrated in other studies. For example, rats administered 0.1 and 1.0 ppm lead acetate in drinking water beginning at weaning through 18 months of age exhibited an approximate 14-mmHg elevation in blood pressure from 3 months (1 ppm) or 12 months (0.1 ppm) through the entire 18 months of exposure (Perry et al. 1988). No obvious signs of toxicity were observed in these animals.

Low-level, chronic-duration exposure of rats to lead (30 ppm lead acetate in the drinking water) for 18 months resulted in a 10–15-mmHg increase in both systolic and diastolic blood pressure without any change in heart rate or histopathological evidence of damage to the kidney, heart, brain, aorta, or liver (Carmignani et al. 1988a). However, the authors were able to demonstrate that lead exposure in these animals increased their responsiveness to stimulation of α and ß receptors, altered the renin-angiotensin system, perhaps through inhibition of the renin-angiotensin converting enzyme, and altered the cyclic adenosine monophosphate (cAMP)-dependent contractile processes in both myocardium and vascular myocells. Please refer to Section 2.4 for a more complete discussion of the proposed mechanisms for lead-induced hypertension.

Cardiovascular effects other than effects on blood pressure have also been observed in laboratory animals following ingestion of lead. Male rats given 1% (10,000 ppm) lead acetate in their drinking water from 6 to 12 weeks of age had changes in the myocardium (including myofibrillar fragmentation and separation with edema fluid), dilation of the sarcoplasmic reticulum, and mitochondrial swelling (Asokan 1974). Blood lead levels in these rats averaged 112 μg/dL, versus 5 μg/dL in controls. The highest NOAEL values and all reliable LOAEL values for each study for cardiovascular effects are recorded in Table 2-4 and plotted in Figure 2-2.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans or animals after oral exposure to inorganic lead. See Section 2.2.1.2 for a discussion of the gastrointestinal effects of lead in humans after multi-route exposure.

Hematological Effects. As discussed in Section 2.2.1.2, lead has long been known to affect heme biosynthesis by affecting the activities of several enzymes in the heme biosynthetic pathway. The mechanisms for these effects are discussed in detail in Section 2.4. Two experimental studies of the effects of oral exposure to lead on heme synthesis in humans were available. Two groups of five women and one group of five men who ingested lead acetate at 0.02 mg lead/kg/day every day for 21 days experienced decreases in erythrocyte ALAD by day 3 of lead ingestion (Stuik 1974). The decreases became maximal by day 14 and then remained constant through day 21. An increase in EP occurred in the women, but not in the men, starting after 2 weeks of ingestion. Blood lead levels were approximately 15 μg/dL before exposure and increased to approximately 40 μg/dL during exposure. Increased EP was observed in five men at a higher dosage, 0.03 mg lead/kg/day (which produced a mean blood lead level of 46 μg/dL), starting after 2 weeks of lead ingestion (Stuik 1974). Similar results were reported by Cools et al. (1976) for 11 men ingesting lead acetate at an initial dosage of 0.03 mg lead/kg/day, which was decreased to 0.02 mg lead/kg/day or less as necessary to maintain a blood lead level of 40 μg/dL; the mean pre-exposure blood lead level was 17.2 μg/dL.

Intermediate-duration studies in animals indicate that adverse hematological effects (i.e., decreased hematocrit, impaired heme synthesis) occur following oral exposure (Krasovskii et al. 1979; Overmann 1977; Walsh and Ryden 1984). The lowest dose at which these effects are seen depends on the route of exposure and the nature of the end point studied. For example, decreases in hematocrit were observed in rats that received 19.2 mg lead/kg/day by gavage (Overmann 1977), but this effect was not seen until a dose of 318 mg lead/kg/day was administered to rats in their daily diet (Walsh and Ryden 1984). Rats that received up to 34 mg lead/kg/day as lead acetate in their drinking water exhibited no adverse effects on hematocrit (Fowler et al. 1980; Victery et al. 1982b). However, evidence of impaired heme synthesis (increased urinary ALA and coprophobilinogen) was observed in rats that received 0.01 mg lead/kg/day as lead acetate in their drinking water (Krasovskii et al. 1979). A similar correlation between exposure to lead in the drinking water as lead acetate and increased urinary ALA was observed by Fowler et al. (1980). Increased urinary ALA and erythrocyte ZPP were also correlated with increasing doses of lead in rats receiving 0, 1.67, or 6.35 mg lead/kg/day in their drinking water (Cory-Slechta 1990b). The increase was observed earlier in the course of the study in older rats.

Adverse hematological effects have been noted in chronic-duration studies, as well. The effects appear to increase in severity with increasing dose. For example, dose (blood lead)-effect information for heme synthesis and hematological effects is available; rats and dogs were fed lead acetate in the diet for 2 years (Azar et al. 1973). In rats, lead produced no effects at 10 ppm (blood lead level = 11.0 μg/dL; not elevated above controls), significant inhibition of ALAD at ≥50 ppm (blood lead level ≥18.5 μg/dL), significant increase in urinary ALA at ≥500 ppm (blood lead level ≥77.8 μg/dL), and slight but significant decreases in hemoglobin concentration and hematocrit at ≥1,000 ppm (blood lead level ≥98.6 μg/dL). In dogs, lead produced no effects at ≤50 ppm (blood lead level ≤31.5 μg/dL), significant inhibition of ALAD at ≥100 ppm (blood lead level ≥42.5 μg/dL), and no effect on urinary ALA, hemoglobin, or hematocrit at any exposure level (highest exposure level = 500 ppm, blood lead level = 75.8 μg/dL). Control blood lead levels were 12.7 and 16.4 μg/dL in the two rat groups and 15.8 μg/dL in the dogs.

Studies in animals indicate that the effects of lead on heme synthesis occur in many tissues. Oral exposure of rats to lead decreased liver ALAS activity (Silbergeld et al. 1982), increased spleen ALAS activity (Silbergeld et al. 1982), decreased kidney ALAS activity (Fowler et al. 1980), decreased brain (Gerber et al. 1978), liver, and spleen (Silbergeld et al. 1982) ALAD activity, and decreased kidney ferrochelatase activity along with mitochondrial injury and disturbance of mitochondrial function (Fowler et al. 1980). The highest NOAEL values and all reliable LOAEL values for each study for hematological effects are recorded in Table 2-4 and plotted in Figure 2-2.

Musculoskeletal Effects. Several case reports of individuals who experienced high exposures to lead either occupationally or through the consumption of illicit whiskey described the occurrence of a bluish-tinged line in the gums (Eskew et al. 1961; Pagliuca et al. 1990). The etiology of this "lead line" has not been elucidated. Individuals having high exposures to lead have also been reported to complain of muscle weakness, cramps, and joint pain (Holness and Nethercott 1988; Marino et al. 1989; Matte et al. 1989; Pagliuca et al. 1990).

No studies were located regarding musculoskeletal effects in animals after oral exposure to inorganic lead.

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to inorganic lead. See Section 2.2.1.2 for a discussion of hepatic effects in humans following multi-route exposure to inorganic lead.

TABLE 2-4. Levels of Significant Exposure to Lead - Oral

Key to figure[a]	Species		Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form[b]
ACUTE EXPOSURE									
Systemic									
1	Human	(C)	3-14 d 7d/wk 1x/d	Hemato		0.02 (decreased ALAD activity)		Stuik 1974	PbAc
2	Human	(C)	5 d 1x/d	Hemato		0.03 (24-61% decrease in ALAD activity)		Cools et al. 1976	PbAc
3	Rat	(F)	1-2 wk ad lib	Other		734.7 (blockage of calcium intestinal transport response to vitamin D)		Smith et al. 1981	PbAc
Immunological									
4	Mouse	(G)	14 d 7d/wk 1x/d			2.6 (decreased spleen and thymus weight, leukopenia)		Hillam and Ozkan 1986	$Pb(NO_3)_2$
Neurological									
5	Rat	(GW)	9,12,15, 18 d post-natal; 1x/d			50 (impaired latent learning)		Massaro and Massaro 1987	PbAc
Developmental									
6	Rat	(GW)	11 d 1x/d Gd6-16				390 (increased fetal resorptions, retarded skeletal development, maternal toxicity)	Kennedy et al. 1975	PbAc

TABLE 2-4 (Continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form[b]
Reproductive								
7	Rat (GW)	11 d 1x/d Gd6-16		39		390 (decreased number of pregnancies)	Kennedy et al. 1975	PbAc
INTERMEDIATE EXPOSURE								
Systemic								
8	Human (C)	21 d 7d/wk 1x/d	Hemato		0.02 (decreased ALAD activity; increased protoporphyrin IX in RBC of females)		Stuik 1974	PbAc
9	Human (C)	7 wk 7d/wk 1x/d	Hemato		0.01-0.03 (decrease ALAD activity; increased RBC porphyrin)		Cools et al. 1976	PbAc
10	Rat (W)	2-3 mo 7d/wk ad lib	Renal	446	892 (increased urinary excretion of B2-microglobulin)	892 (proximal tubular dysfunction)	Vyskocil et al. 1989	PbAc
11	Rat (F)	7-8 wk 7d/wk	Hemato		318 (decreased hematocrit)		Walsh and Ryden 1984	PbAc
			Renal		318 (increased kidney weight)			
			Other		318 (decreased body weight)			
12	Rat (W)	20-30 d 1x/d ad lib	Hepatic		0.05 (decreased RNA, glycogen; pyknosis of Kupffer cells; increased weight)		Krasovskii et al. 1979	PbAc

TABLE 2-4 (Continued)

Key to figure[a]	Species		Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form[b]
13	Rat	(W)	6 wk ad lib	Cardio		873 (myofibrillar fragmentation, mitochondrial swelling)		Asokan 1974	PbAc
14	Rat	(W)	6-12 mo ad lib	Hemato	0.002	0.01 (impaired heme synthesis)		Krasovskii et al. 1979	PbAc
				Hepatic	0.002	0.01 (decreased glycogen, RNA, sulfhydryl groups, alterations in activities of oxidizing enzymes)			
15	Rat	(W)	3 wk ad lib	Derm/oc		0.5 (rod degeneration)		Fox and Chu 1988	PbAc
16	Rat	(W)	3 wk ad lib	Derm/oc		0.5 (alterations in rod photoreceptors)		Fox and Farber 1988	PbAc
17	Rat	(W)	3 wk ad lib	Derm/oc		0.5 (decreased retinal sensitivity, rhodopsin, and rod outer segment length)		Fox and Rubinstein 1989	PbAc
18	Rat	(W)	159 d ad lib	Cardio	0.03	0.3 (increased systolic blood pressure)		Perry and Erlanger 1978	PbAc
19	Rat	(GW)	18 d 1x/d	Hemato	6.4	19.2 (decreased hematocrit)		Overmann 1977	PbAc

TABLE 2-4 (Continued)

Key to figure[a]	Species		Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form[b]
20	Monkey	(GW)	174 d (2 d at 10 mg/kg) (12 d at 3 mg/kg) (160 d at 0.7 mg/kg 1x/d	Hemato	0.7	10 (increased ZPP)		Levin et al. 1988	PbAc
Neurological									
21	Rat	(W)	112 d ad lib		14.3			Massaro and Massaro 1987	PbAc
22	Rat	(W)	35 d ad lib			1.6 (reduced radial maze accuracy)		Bushnell and Levin 1983	
23	Rat	(G)	10 wk (from PND1 or PND5) 5d/wk 1x/d			1.0 (neurochemical changes)		Singh and Ashraf 1989	PbAc
24	Rat	(W)	186 d ad lib			2.1 (higher response rate for operant learning tests)		Cory-Slechta et al. 1985	PbAc
25	Rat	(GW)	18 d 1x/d		6.4		19.2 (increased motor activity and operant delayed response)	Overmann 1977	PbAc
26	Rat	(G)	10 wk (from PNW5) 5d/wk 1x/d		1.0			Singh and Ashraf 1989	PbAc

TABLE 2-4 (Continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form[b]
27	Rat (W)	6-12 mo ad lib		0.002	0.01 (disruption of conditioned responses and motor activity)		Krasovskii et al. 1979	PbAc
28	Rat (W)	15 wk ad lib			89.6 (decrease in motor nerve conduction velocity)		Yokoyama and Araki 1986	PbAc
29	Rat (W)	335 d ad lib			9.5 (increased fixed interval response rates to lever press)		Cory-Slechta et al. 1983	PbAc
30	Monkey (GW)	174 d (2 d at 10 mg/kg, 12 d at 3 mg/kg, 160 d at 0.7 mg/kg) 1x/d			0.7-10 (lower muscle tonus; decreased visual attentiveness)		Levin et al. 1988	PbAc trihydrate
31	Monkey (G)	357 d (2 d at 10mg/kg, 12 d at 3 mg/kg, 343 d at 0.7 mg/kg) 1x/d				0.7-10 (impaired open field behavior, behavioral alterations)	Ferguson and Bowman 1990	PbAc
32	Monkey (F)	344-362d 7d/wk 1x/d				0.29 (deficit in reversal learning)	Bushnell and Bowman 1979b	PbAc
33	Monkey (GW)	200 d 1x/d 5d/wk			0.05 (impaired nonspatial discrimination at 3 years of age)		Rice 1985b	PbAc

TABLE 2-4 (Continued)

Key to figure[a]	Species		Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form[b]
34	Monkey	(GW)	200 d 5d/wk 1x/d			0.1 (impaired spatial discrimination reversal task at 9-10 years of age)		Gilbert and Rice 1987	PbAc
35	Monkey	(F)	344-362 d 1x/d			0.3 (deficit in reversal learning tasks)		Bushnell and Bowman 1979a	PbAc
36	Monkey	(GW)	195-210 d Gd1-165 1x/d				3 (deficit in form discrimination at 6-18 months and in response to inhibition at 19-29 months in offspring)	Hopper et al. 1986	$Pb(NO_3)_2$
Developmental									
37	Rat	(W)	84-91 d ad lib			3.5 (delayed vaginal opening)		Kimmel et al. 1980	PbAc
38	Rat	(W)	27-39 wk ad lib		0.7	3.5 (delayed vaginal opening in pups)		Grant et al. 1980	PbAc
39	Rat	(W)	63 d ad lib		0.09	0.9 (decreased ALAD activity, increased protoporphyrins in pups)		Hubermont et al. 1976	$Pb(NO_3)_2$
40	Rat	(W)	56 d ad lib				28 (delayed cortical development in pups)	McCauley et al. 1979	$PbCl_2$
41	Rat	(W)	56 d Gd1-21 ad lib				28 (learning deficit)	Taylor et al. 1982	PbAc

TABLE 2-4 (Continued)

Key to figure[a]	Species		Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form[b]
42	Rat	(W)	Gd1-21 5 mo			2.2 (inhibit renin synthesis and release)		Victery et al. 1982a	PbAc
43	Rat	(GW)	41 d 1x/d Gd1-21			64 (decreased fetal weight)		Miller et al. 1982	PbAc
44	Rat	(W)	18-21 d ad lib Gd1-18, 21			0.7 (impaired heme synthesis in pups)		Hayashi 1983	PbAc
45	Rat	(W)	138-145 d 2 gen				0.7 (impaired righting reflex in pups)	Reiter et al. 1975	PbAc
46	Rat	(W)	105-112 d 1x/d Gd1-21				3.5 (immune suppression; decreased thymus weight in pups)	Luster et al. 1978	PbAc
47	Rat	(W)	Gd1-21 312 d ad lib		0.07	0.7 (elevated kidney weight, cyto-megaly in male pups)		Fowler et al. 1980	PbAc
48	Rat	(W)	105-115 d ad lib Gd1-21			3.5 (decreased thymic weight in pups)	3.5 (suppression of delayed hyper-sensitivity response and lymphocyte responsiveness to mitogen stimulation)	Faith et al. 1979	PbAc

TABLE 2-4 (Continued)

Key to figure[a]	Species		Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form[b]
49	Rat	(W)	56 d ad lib			25-45 (maternal dose) (delayed synthesis of cytochrome C in cerebral cortex in male pups neonatally exposed)		Bull et al. 1979	$PbCl_2$
50	Rat	(W)	3 wk 7d/wk ad lib			15 (alteration of hippocampal components in offspring)		Slomianka et al. 1989	PbAc
51	Gn pig	(GW)	30,40 d 1x/d Gd22-52			5.5 (decrease in the neuroglial enzymes GPDH and glutamine synthetase, impaired heme synthesis in pups and dams)		Sierra et al. 1989	PbAc
52	Mouse	(W)	41 d Gd1-21 ad lib				608 (behavioral changes in offspring)	Draski et al. 1989	PbAc
53	Monkey	(W)	8.5 mo Gd1-165 ad lib		3.8			Levin and Bowman 1983	PbAc
Reproductive									
54	Rat	(W)	6-12 mo ad lib		0.002	0.01 (enzyme changes and swelling of follicular epithelial cells in males)		Krasovskii et al. 1979	PbAc
55	Rat	(W)	312 d 7d/wk ad lib		34			Fowler et al. 1980	PbAc

TABLE 2-4 (Continued)

Key to figure[a]	Species		Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form[b]
56	Rat	(G)	30 d 1x/d			0.013 (males: increased prostate weight)	0.26 (males: impotence; hyperplasia; increase prostate weight)	Hilderbrand et al. 1973	PbAc
						0.014 (females: irregular estrus cycles)	0.26 (females: ovarian cysts; persistent vaginal estrus)		
57	Rat	(W)	63 d ad lib		0.9			Hubermont et al. 1976	$Pb(NO_3)_2$
58	Rat	(W)	20-30 d ad lib		0.002	0.01 (dystrophy of Leydig cells)	0.05 (decreased motility of spermatozoa, acid phosphatase activity increased)	Krasovskii et al. 1979	PbAc
59	Rat	(W)	60 d ad lib		22	45 (partial inhibition of spermatogenesis)	90 (testicular atrophy, cellular degeneration)	Chowdhury et al. 1984	PbAc
60	Rat	(W)	30 d ad lib			40 (decreased LH and prolactin levels)		Sourgens et al. 1987	PbAc
61	Rat	(GW)	9 wk 7d/wk 1x/d				0.19 (decreased number of spermatozoa)	Barratt et al. 1989	PbAc
62	Mouse	(W)	38 wk 7d/wk ad lib		19			Donald et al. 1986a	PbAc
63	Mouse	(W)	12 wk 7d/wk 1x/d				141 (decreased number of implantations)	Johansson and Wide 1986	$PbCl_2$

TABLE 2-4 (Continued)

Key to figure[a]	Species		Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form[b]
CHRONIC EXPOSURE									
Systemic									
64	Rat	(W)	76 wk ad lib	Renal			37 (cortical necrosis and dilation)	Koller et al. 1985	PbAc
65	Rat	(W)	<18 mo 7d/wk 1x/d	Cardio		0.01 (increase in systolic blood pressure)		Perry et al. 1988	
				Other	0.45				
66	Rat	(W)	18 mo 7d/wk 1x/d	Cardio	1.4	2.8 (increased systolic and diastolic blood pressure)		Carmignani et al. 1988a	PbAc
67	Rat	(F)	2 yr ad lib	Hemato	0.9	3.1 (decreased ALAD activity)		Azar et al. 1973	PbAc
68	Dog	(F)	2 yr ad lib	Hemato	1.25	2.5 (decreased ALAD activity)		Azar et al. 1973	PbAc
				Renal	2.5	12.5 (cytomegaly in males)			
69	Monkey	(F)	1 yr 7d/wk 1x/d	Hemato	0.57			Mele et al. 1984	PbAc
				Other	0.57				
Neurological									
70	Dog	(F)	2 yr 7d/wk ad lib		12.5			Azar et al. 1973	PbAc
71	Monkey	(C)	7-8 yr 5d/wk 1x/d				0.05 (impairment in delayed alternation behavioral task)	Rice and Karpinski 1988	PbAc

TABLE 2-4 (Continued)

Key to figure[a]	Species		Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form[b]
72	Monkey	(G)	200-270 d 7d/wk 1x/d				0.05 (impaired operant learning)	Rice 1985b	
73	Monkey	(F)	1 yr 7d/wk 1x/d			0.21 (reversal learning deficit; electro-physiological changes in auditory process)		Laughlin et al. 1983	PbAc
74	Monkey	(F)	1 yr 7d/wk ad lib		0.64			Levin and Bowman 1989	PbAc
Reproductive									
75	Monkey	(W)	75 mo 5d/wk			1.3-5 (impaired menstrual cycle)		Franks et al. 1989	PbAc
Cancer									
76	Rat	(F)	2 yr 7d/wk ad lib				27 (5/50 renal tumors in males)	Azar et al. 1973	PbAc
77	Rat	(W)	76 wk ad lib				37 (CEL; renal tumors in 13/16)	Koller et al. 1985	PbAc
78	Mouse	(F)	2 yr ad lib				83.2 (CEL-renal tumors in 7/25)	Van Esch and Kroes 1969	PbAc

[a]The number corresponds to entries in Figure 2-3.
[b]If not specified, not known

ad lib = ad libitum; ALAD = delta-aminolevulinic acid dehydratase; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Derm/oc = dermal/ocular; (F) = feed; (G) = gavage; Gd = gestation day(s); GPDH = glucose-6-phosphate dehydrogenase; gen = generation(s); Gn pig = guinea pig; (GW) = gavage in water; Hemato = hematological; LH = luteinizing hormone; LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; PbAc = lead acetate; $PbCl_2$ = lead chloride; $Pb(NO_3)_2$ = lead nitrate; PND = post natal day; PNW = post natal week; RBC = red blood cells; RNA = ribonucleic acid; (W) = drinking water; wk = week(s); x = time(s); yr = year(s); ZPP = zinc protoporphyrin

FIGURE 2-2. Levels of Significant Exposure to Lead - Oral

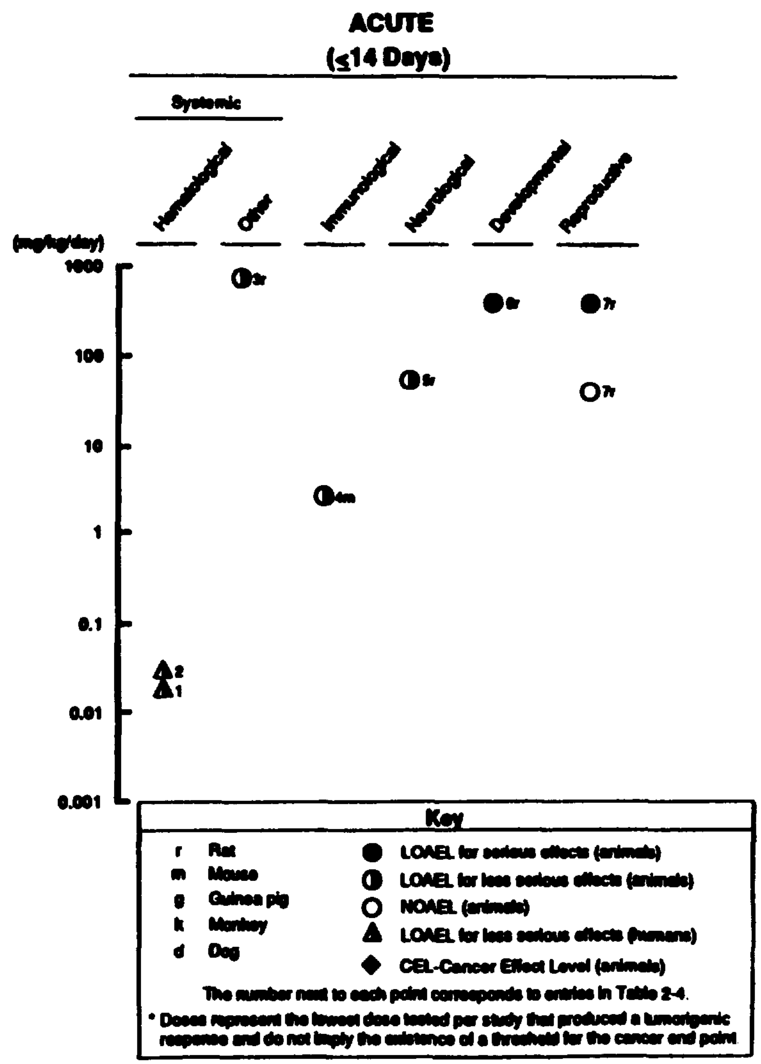


FIGURE 2-2 (Continued)

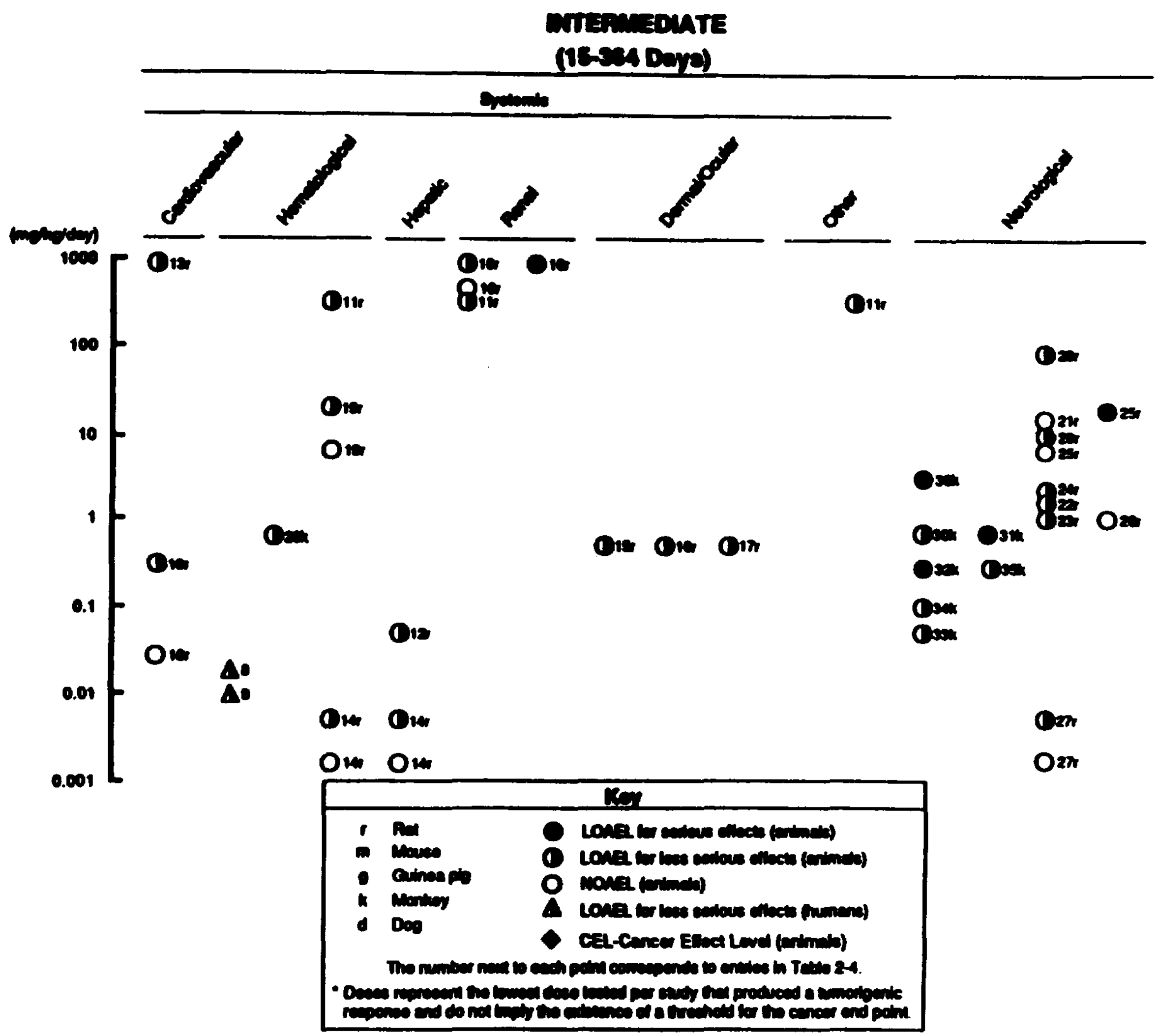


FIGURE 2-2 (Continued)

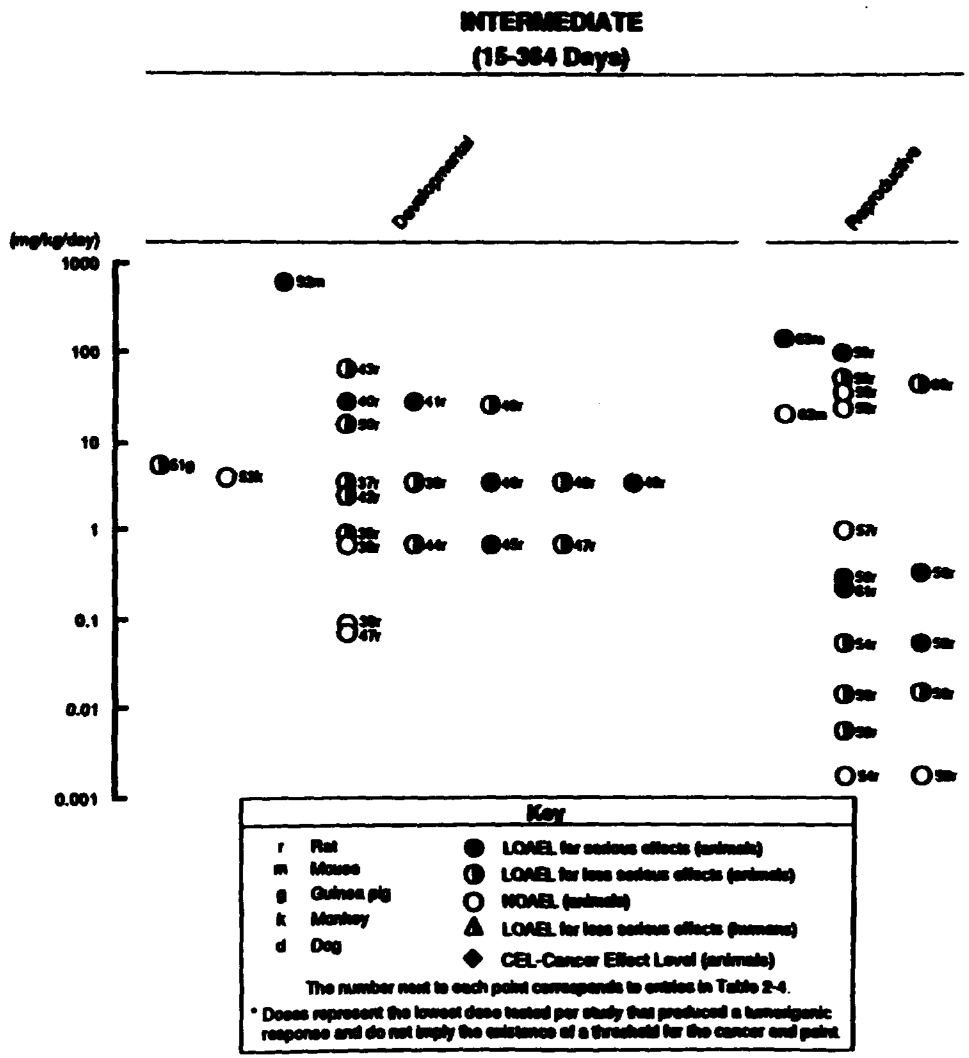
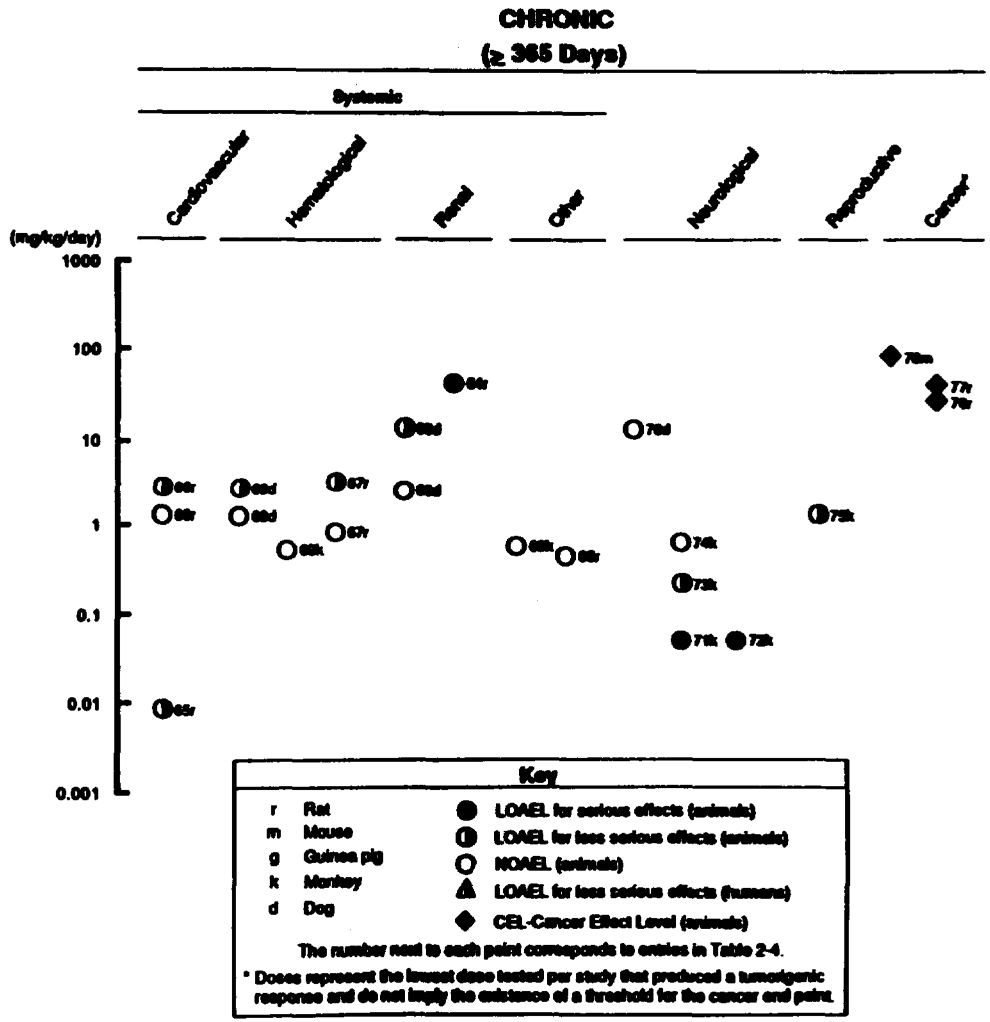


FIGURE 2-2 (Continued)



The effects of intermediate-duration dietary lead administration on the liver of rats were studied by Giurgea et al. (1989). Several parameters of hepatic function were studied in male Wistar rats fed a basal diet and in animals administered 10 mg lead acetate each in the daily feed for 28 days and kept either on a normal light/dark cycle or kept continuously in the dark. Hepatic glycogen and deoxyribonucleic acid (DNA) content were reduced and total protein and ribonucleic acid (RNA) content were increased in both groups of lead-exposed animals. However, only the changes in total protein and glycogen were statistically significant. The effects appeared to be more pronounced in the lead+dark animals. The authors conclude that their results suggest that lead adversely affects the liver following intermediate-duration dietary exposure in rats. The toxicological significance of the changes observed, however, are unknown, given the nonspecific nature of the end points measured and the fact that no histopathological evaluation or organ function tests were conducted. Therefore, this study has not been included in Table 2-4.

Liver toxicity, as evidenced by alterations in the incorporation of lysine into liver proteins, was observed in rats administered 192 mg lead/kg/day by gavage as lead acetate for 9 weeks (Barratt et al. 1989). No effects were observed at 21 mg lead/kg/day. However, the toxicological significance of this finding is not known because neither serum enzymes nor histopathological evaluations were performed.

Intermediate-duration exposure to 0.01 mg lead/kg/day as lead acetate in the drinking water of rats resulted in increased liver weight, decreases in RNA and glycogen, pyknosis of Kupffer cells, and decreased enzyme activity (e.g., lactate dehydrogenase) (Krasovskii et al. 1979). This LOAEL is presented in Table 2-4 and plotted in Figure 2-2.

Renal Effects. Ingestion of drinking water containing lead was found to be associated with evidence of renal insufficiency in humans (Campbell et al. 1977). Lead concentrations in drinking water were compared to blood lead concentrations in 283 residents who ingested this water for a mean of 21.5 years. A highly significant correlation was found for these two parameters. In addition, elevated blood lead concentrations were associated with renal insufficiency, reflected as raised serum urea concentrations and hyperuricemia. No renal biopsies were performed.

Information is available on the renal toxicity of ingested lead in several species, including rats, dogs, monkeys, and rabbits. The results indicate that histopathological changes in the kidneys of lead-treated animals are similar to those in humans (see Section 2.2.4.2), except that glomerular lesions were not reported in the animal studies. Reduced glomerular filtration rates and aminoaciduria were reported in some of the animal studies. A few of the key animal studies on lead-induced renal toxicity will be discussed below.

Dose (blood lead)-effect data are available in the study by Fowler et al. (1980). Rats exposed to lead acetate in the drinking water through the dams during gestation and lactation and then directly until 9 months of age had the following external exposures (ppm lead), internal exposures (μg lead/dL in blood), and renal effects: 0 ppm (controls), 5 μg/dL, no lesions; 0.5 ppm, 4.5 μg/dL, no lesions; 5 ppm, 11 μg/dL, cytomegaly; 50 ppm, 26 μg/dL, cytomegaly, intranuclear inclusion bodies, and swollen mitochondria; 250 ppm, 67 μg/dL, cytomegaly, intranuclear inclusion bodies, swollen mitochondria, and hemosiderin. These effects occurred in the proximal tubule cells; no lesions were seen in the glomeruli. No evidence of interstitial reaction or of tumor formation was seen.

Similar results were obtained by Vyskocil et al. (1989) who studied the effects of intermediate-duration administration of lead in the drinking water of male Wistar rats on renal function. Administration of 446 mg lead/kg/day was without effect. An increase in the urinary excretion of β_2-M was seen in the animals that received 892 mg lead/kg/day. Animals treated with 1,783 mg lead/kg/day exhibited increased urinary excretion of β_2-M, glucose, total proteins, lysozyme, and lactate dehydrogenase (LDH) levels. Examination of the kidneys revealed no treatment-related changes in the 446-mg/kg/day group, and morphological changes primarily in the epithelial cells of the proximal tubules in the 892- and 1,783-mg kg/day groups that were characterized by intranuclear inclusion bodies and enlarged nuclei. Hyperplasia and flattening of the proximal tubular epithelium were also observed. Based on these results, exposure to lead acetate at levels of ≥892 mg lead/kg/day in the drinking water results in proximal tubular dysfunction in rats. However, histopathological changes were noted in the kidneys of rats administered lead acetate in the drinking water for 76 weeks at lower doses (Koller et al. 1985). These changes, which were observed at a dose of 37 mg/kg/day, included necrotic and dilated cortical tubules, tubular protein casts, areas with large nuclei and fibrous connective tissue, and large intranuclear inclusion bodies in the enlarged epithelial cells of the cortex near the cortical-medullary junction. The highest NOAEL values and all reliable LOAEL values for each study for renal effects are recorded in Table 2-4 and plotted in Figure 2-2.

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans after oral exposure to inorganic lead. See Section 2.2.1.2 for a discussion of dermal/ocular effects in humans following multi-route exposure to inorganic lead.

Long-term scotopic visual system deficits have been observed in laboratory animals following low-level lead exposure during early postnatal development (Fox et al. 1982). To determine whether this was due to an effect of lead on the central nervous system or a direct effect of lead on the eye, a series of experiments were performed by Fox and coworkers to determine the effects of low-level lead exposure on ocular function during early postnatal development in rats (Fox and Chu 1988; Fox and Farber 1988; Fox and Rubinstein 1989). In the first study, timed-pregnant hooded rats were administered lead acetate in the drinking water from day of birth (day 0) through lactation (day 21). The authors state that results from previous studies show that rat pups receive 0.5 mg/kg/day of lead through the milk under such an exposure regimen. At weaning the animals were transferred to standard laboratory chow and maintained until 90 days of age. At this point, acute (single flash) electroretinograms (ERG) and cyclic nucleotide metabolism studies were conducted. The blood lead levels in the lead-exposed pups were 59 μg/dL at 21 days of age and 7 μg/dL at 90 days of age. The results of the single-flash ERGs indicated that lead exposure caused a significant decrease in amplitude, a significant increase in latency, and a significant decrease in sensitivity in various waveforms suggesting that low-level lead exposure during postnatal development has a selective detrimental effect on the rods of the retina. The authors speculated on the mechanism of such a change. One possibility is that lead alters cyclic nucleotide metabolism such that the activity of the sodium channels in the rods is changed. To investigate this possibility, cyclic nucleotide content and the activity of the enzymes associated with their metabolism were measured. A significant increase in cyclic guanosine monophosphate (cGMP), but not cyclic adenosine monophosphate (cAMP) was found in both light- and dark-adapted lead-exposed animals as compared to the controls. This increase in cGMP content was in turn found to be associated with decreased cGMP-phosphodiesterase (PDE) activity (Fox and Farber 1988).

A similar exposure regimen was employed in the second study (Fox and Chu 1988) to study the effects of low-level lead exposure on the ultrastructure and quantitative histology of the retina during early postnatal development in rats. At weaning the animals were transferred to standard laboratory chow and maintained until 90 days of age. At this point, the animals were sacrificed, and the retinas were removed for light and electron microscopic analysis. The authors found that there was a selective degeneration of rod (but not cone) photoreceptor cells in the lead-exposed rats, leading to an overall loss of 20% of rod cells. Degeneration occurred more in the inferior than the superior retina, and more in the posterior than the peripheral retina. The outer and inner nuclear layers were also reduced in thickness in the lead exposed-rats. General retinal damage was evidenced by the accumulation of glycogen particles in the lead-exposed rats. These results support the hypothesis posed by Fox and Farber (1988) that low-level lead exposure during postnatal development has a selective detrimental effect on the rods of the retina.

In the third study, rats were exposed in the same manner as the two previous studies to evaluate the effects of low-level lead exposure on retinal sensitivity, rhodopsin content, and rod outer segment length throughout the 1st year of life in rats exposed during early postnatal development (Fox and Rubinstein 1989). The authors found that retinal sensitivity and rhodopsin content in the lead-exposed rats was decreased at all ages tested. There was no change in the λ_{max} of the rhodopsin in the lead-exposed animals as compared to the control animals. Histological evaluation revealed that there was a decrease in rod outer segment length coupled with a selective loss of 20% of the rod cells which would account for the decrease in rhodopsin content in the lead-exposed rats. The results also indicate that most of these effects occur within the first 30 days of life, although the changes remain throughout the 1st year. Taken together, the results of these three studies strongly suggest that low-level lead exposure during postnatal development has a selective detrimental effect on the rods of the retina. The LOAELs from these studies are recorded in Table 2-4 and plotted in Figure 2-2.

Other Systemic Effects. No studies were located regarding other systemic effects in humans after oral exposure to inorganic lead. See Section 2.2.1.2 for a discussion of other systemic effects of lead in humans after multi-route exposure to lead.

Depression of plasma levels of 1,25-dihydroxyvitamin D was observed in rats fed 0.82% lead in the diet as lead acetate for 7–14 days (Smith et al. 1981). This LOAEL is recorded in Table 2-4 and plotted in Figure 2-2. High calcium diets protected against this effect. An additional finding was that lead blocked the intestinal calcium transport response to exogenous 1,25-dihydroxyvitamin D but had no effect on bone response to the vitamin D hormone. Although the lead exposure and resulting blood lead levels ($\geq$174 μg/dL) were high in this study, the results provide support for the disturbances in vitamin D metabolism observed in children exposed to high levels of lead (described in Section 2.2.1.2).

2.2.3.3 Immunological Effects

No studies were located regarding immunological effects in humans after oral exposure to inorganic lead. See Section 2.2.1.3 for a discussion of immunological effects of lead in humans after multi-route exposure to lead.

Low-level exposure of rats to lead has resulted in adverse effects on both the humoral and cellular components of the immune system. Prenatal and postnatal exposure of rats to 3.5 mg lead/kg/day as lead acetate in the drinking water (indirectly through the dams and then directly) until testing at 35–45 days of age resulted in a mean blood lead level of 29.3 μg/dL and marked depression of antibody responses to sheep red blood cells, decreased serum IgG (but not IgA or IgM) levels, decreased lymphocyte responsiveness to mitogen stimulation, impaired delayed hypersensitivity reactions, and decreased thymus weights as compared with controls. The 3.5-mg lead/kg/day dose was the lowest level tested (Faith et al. 1979; Luster et al. 1978).

The effects of intermediate-duration dietary lead administration on the thymus of rats administered lead acetate in the feed and kept in a normal light/dark cycle or kept continuously in the dark was studied by Giurgea et al. (1989). Thymus weight was significantly reduced in the lead-exposed animals, but the difference was not statistically different in the lead+dark animals. Alternatively, total protein content in the thymus was significantly reduced in the lead+dark animals but not in the lead-exposed animals, while DNA and glycogen content were significantly increased in both lead-exposed groups. Since the weight of the adrenal gland was not affected by lead, the authors concluded that the changes in the thymus may be a direct effect of lead rather than a result of adrenal activation by stress, and that their results suggest that lead adversely affects components of the immune system (i.e., the thymus) following intermediate-duration dietary exposure in rats. The toxicological significance of the changes observed, however, are unknown, given the nonspecific nature of the end points measured and the fact that no histopathological evaluation or organ function tests were conducted. Therefore, this study is not included in Table 2-4.

Other investigators have been unable to demonstrate lead-induced effects on various components of the immune system in laboratory animals. The effects of lead exposure of varying duration on natural killer cell and T-lymphocyte function were investigated in rats. Male Alderly Park rats received lead as lead acetate in the drinking water at lead concentrations equivalent to 14.3 and 143 mg lead/kg/day for 1–8 weeks (Kimber et al. 1986a). Every week starting at 1 week of exposure, two rats were killed and the spleens and thymus glands were removed. Blood lead concentrations were <9 μg/dL in the control animals, 5–14 μg/dL in the low-dose animals, and 15–45 μg/dL in the high-dose animals. The activity of ALAD was also measured as an indicator of lead toxicity and was substantially inhibited (27% and 43% inhibition for the low-dose and high-dose animals, respectively). Lead exposure had no effect on the weight of the spleen or thymus. There was no difference between the control and lead-exposed natural killer cells with respect to cytotoxic capacity or interferon-induced potentiation of cytotoxic activity. Furthermore, there was no effect of lead on the proliferative response of T-lymphocytes to phytohemagglutinin. Thus, it appears that exposure to lead at levels that inhibit ALAD has no effect on certain components of the cellular immune function (e.g., natural killer cells and T-lymphocytes). However, the conclusions that can be reached based on the results of the Kimber et al. (1986a) study are limited in that only two animals were examined per time point. Therefore, it is not surprising that no treatment-related effects were observed, given the known differences in susceptibility to lead, particularly at low levels of exposure where considerable overlap of control and lead distributions would be expected.

Similarly, oral lead exposure had little effect on local and systemic immune function following intratracheal, intraperitoneal, or intravenous immunization with sheep red blood cells in mice (Hillam and Ozkan 1986). Eight mice (sex not specified) per group were administered 2.6 mg lead/kg/day as lead nitrate. Eight mice administered deionized water served as controls. The following parameters of immune function were measured in the immunized, lead-exposed mice: differential and total leukocyte counts (measure of systemic cellular immune function), hemagglutination titers (measure of systemic humoral immune function), and antibody forming cells (AFC) counts in the thoracic lymph nodes and the spleen (measure of both local and systemic immune function). Splenic and thymic organ weights were also determined, as well as tissue lead content. Lead content was similar to the controls in all tissues. Both splenic and thymic weights were significantly decreased in the lead-exposed animals as compared to the controls. Total leukocyte count was significantly decreased in the lead-exposed animals, but no change in the differential leukocyte counts was observed. Intraperitoneal immunization did not result in a significant decrease in the antibody titers of the lead-exposed animals as it did when mice were exposed by inhalation for 28 days. Regardless of the route of immunization, oral administration of lead did not affect the number of AFCs in either the spleen or the thoracic lymph node. Based on these results, orally administered lead does not induce immunosuppression as it did when inhaled (see Section 2.2.2.3). This difference may be attributed to the fact that lead is more readily absorbed from the lung than the gut. A LOAEL for immunological effects is recorded in Table 2-4 and plotted in Figure 2-2.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to inorganic lead. See Section 2.2.1.4 for a discussion of neurological effects of lead in humans after multi-route exposure to lead.

The literature on the neurobehavioral effects of oral exposure to lead in animals is extensive. Only those studies considered key to clarifying human health issues will be presented here. High levels of exposure to lead produce encephalopathy in several species, but blood lead data for this effect are generally not available.

A number of histopathological studies of lead's effects on the nervous system of rats treated during early postnatal life with lead acetate or carbonate in the drinking water or diet through their dams or directly, for ≤3 weeks, have shown a variety of adverse effects at blood lead levels ranging from 258 to 400 μg/dL. These effects include reductions or delays in the development of the hippocampus or other hippocampal changes (Alfano and Petit 1982; Alfano et al. 1982; Slomianka et al. 1989), reductions or delays in the development of the cerebral cortex (Petit and LeBoutillier 1979), reductions in the number and size of axons in the optic nerve of mice (Tennekoon et al. 1979), and demyelination of peripheral nerves (Windebank et al. 1980).

Cytoarchitectural changes have also been noted in the eyes of monkeys chronically exposed to lead beginning at or shortly after birth (Reuhl et al. 1989). Selected components of the visual system of seven cynomolgus monkeys were studied in an attempt to characterize the neurotoxic effects of long-term exposure to lead. Three infant monkeys were orally administered lead acetate dissolved in glycerin at a dose of 2 mg lead/kg/day starting at 145, 91, and 89 days of age. The exact mode of administration was not specified. Four other infant monkeys received lead acetate in glycerin at daily doses of 0.025 mg lead/kg/day starting at birth. The monkeys were killed at 6 years of age. Blood lead levels for the high-dose group were 90 μg/dL before weaning and 50 μg/dL after weaning. Blood lead levels for the low-dose group were approximately 9 μg/dL. During this time the monkeys participated in a dietary study at which time their blood lead levels were elevated for approximately 100 days. No other details regarding this dietary study were given. The monkeys were killed 36 months after the completion of the dietary study. At this time the high-dose monkeys had maintained steady state blood lead levels of 50 μg/dL for 3 years. Samples of the optic nerve, lateral geniculate body of the brain, and visual areas V1 and V2 from the occipital cortex were taken for morphological analysis. The lateral geniculate body was chosen because it is involved in temporal or spatial visual function. Area V2 represents secondary visual cortex; with area V1, it contributes numerous projections to higher visual centers and involves input from progressively larger visual projection fields. No changes in the optic nerve or the lateral geniculate body were observed using either light microscopy or electron microscopy in either group of monkeys. Quantitative analysis revealed a lower neuronal volume density in the high-dose animals in all regions of areas V1 and V2, but not the lateral geniculate nucleus. Morphometric analysis revealed that the initial branching of neurons in both medial and lateral samples of areas V1 and V2 was inhibited in the high dose-monkeys (Reuhl et al. 1989). While these results suggest that long-term lead exposure may affect neurons in the primary visual cortex, without electrophysiological and/or behavioral assessment of visual function, the toxicological significance of these morphological findings is unknown. The study is limited in that the two groups of animals were subjected to different exposure regimens (the high-dose group was not exposed from birth), which could have influenced the expression of lead-induced toxicity; there were no concurrent controls; the animals participated in a dietary study, and therefore, the exact total exposure of these animals to lead is not known; and only three or four animals were studied per dose group.

A number of neurochemical changes have been observed in the brains of rats exposed both pre- and postnatally to lead (Singh and Ashraf 1989). Pregnant rats were administered lead acetate by gavage in saline 5 times/week after day 14 of gestation at a dose of 1 mg lead/kg/day. After birth, pups were given 1 mg lead/kg/day by gavage 5 days/week for 10 weeks. Brain norepinephrine and γ-aminobutyric acid (GABA) levels and glutamic acid decarboxylase (GAD) activity were decreased, and brain glutamate, glutamine + asparagine, tyrosine levels, and monoaminooxygenase (MAO) activity were increased in the lead-exposed rats. Brain ammonia, alanine, aspartic acid, and dopamine were not affected. Brain uptake values for glutamine were significantly increased. Similar results were observed in pups exposed to 1 mg lead/kg/day, 5 days per week for 10 weeks when exposure was initiated 5 days postnatally, but not when initiated at 5 weeks postnatally. These results suggest that the rapidly developing rat brain may be more susceptible to the neurotoxic effects of lead than the brains of older rats.

Recent studies have focused on neurobehavioral effects of exposure of the developing organisms to lead. Studies concerned primarily with the effects of prenatal exposure are presented in the section on developmental effects (Section 2.2.3.5), while studies concerned primarily with postnatal exposure are discussed here.

Investigations of the development of motor function and reflexes in rats have shown effects at blood lead levels of ≥59 μg/dL. Male rats were treated with lead acetate at 45, 90, or 180 mg lead/kg/day by gavage on postnatal days 3–21 (Kishi et al. 1983). The air righting reflex was significantly delayed at all doses. Eye opening was accelerated at the lowest dose tested, which produced a mean blood lead level of 59 μg/dL. Rotorod performance at postnatal days 53–58 was significantly impaired at the highest dose, which produced a mean blood lead level of 186 μg/dL. An adverse effect of lead on rotorod performance at postnatal days 30–70 was noted in rats treated by gavage on days 3–21 of age with 19.2 mg lead/kg/day as lead acetate, which resulted in a mean blood lead level of 174 μg/dL, but no effect was noted in rats treated with 6.4 mg lead/kg/day as lead acetate, which resulted in a mean blood lead level of 33 μg/dL (Overmann 1977). Thus, neonatal lead exposure produced behavioral effects without causing adverse effects on growth or overt signs of poisoning.

Several studies have reported effects on performance in learning tasks in rats with blood lead levels of <30 μg/dL. The lowest external exposure level that was significantly associated with a behavioral effect in rats was reported by Bushnell and Levin (1983). The authors found that exposure of rats starting at postnatal day 21 (postweaning) to drinking water at 1.6 mg lead/kg/day for 35 days produced a decrease in spontaneous alternation in a radial arm maze. Although the blood lead level was not measured, the mean brain lead level on the day following termination of exposure was 0.05 μg/g. The effects of neonatal exposure to lead on complex maze learning was studied in male Wistar rats. The rats were administered 50 mg lead/kg/day as lead acetate in water by gavage on postgestation days 9, 12, 15, and 18, or 14.3 mg lead/kg/day in the drinking water for 112 days beginning on postgestation day 21 (Massaro and Massaro 1987). Two control groups were included: a vehicle (sodium acetate) control group and an untreated control group. The animals began extensive maze training on day 31 or 143 postpartum and were tested on days 41–45 or 153–157. The parameter studied was latent learning: the animals were trained to run the maze or explore an open field in a satiated condition and in the absence of any positive or negative reinforcement (known as the free exploration phase). Experienced animals as well as unexperienced animals are then placed in the maze following food deprivation. The measure of latent learning is the performance of the experienced animals compared to that of the inexperienced animals. There was no difference between the controls and the lead-exposed animals with respect to activity during the free exploration phase. However, during the food deprivation trial in the maze, the animals exposed to lead during the early postgestation period made significantly more errors, whereas the young adults exposed for

112 days did not. These results indicate that in animals lead exposure alters the ability to transfer information from a previous learning experience in this experimental paradigm but that this effect is not seen in the young adult.

Other types of tests have also revealed behavioral changes in rats exposed to low levels of lead. Significant effects were noted in rats exposed after weaning and throughout the course of the experiment to lead acetate at 2.1 mg lead/kg/day in their drinking water, which resulted in blood lead levels of 15-20 μg/dL (Cory-Slechta et al. 1985). The lead-exposed rats had a significantly higher response rate and a significantly shorter interval between bar-press responses on a fixed-interval operant schedule of food reinforcement. Similar results were obtained at higher exposure levels in a series of earlier studies (Cory-Slechta and Thompson 1979; Cory-Slechta et al. 1981, 1983), even when the operant schedule or contingency for reinforcement was rather different. According to EPA (1986a), a tendency in lead-treated rats to respond more rapidly (higher response rate, shorter inter-response times, shorter response latency) or to respond even when inappropriate (such as when no reward is provided for responses or when reward is specifically withheld for responding) has been reported in many other studies as well, frequently at blood lead levels of <30 μg/dL at the time of testing.

Impairment has also been reported at low blood lead levels in other types of behavior/learning studies in rats. In a test of spatial discrimination, rats were exposed to lead acetate at 745 mg lead/kg/day in the diet indirectly via administration to their dams through gestation and lactation and then directly until testing (at 100 and 200 days of age) (Winneke et al. 1977). The lead-exposed rats were slower to learn the discrimination than were controls. Their blood lead levels at postnatal day 16 averaged 26.6 μg/dL and the levels at 190 days averaged 28.5 μg/dL.

A recent study in rodents has demonstrated that lead (at blood lead levels <30 μg/dL) has a selective effect on learning that is distinct from non-specific performance changes. Male Wistar rats were exposed to lead as lead acetate in drinking water from weaning through the completion of the experiment (Cohen et al.1992). At 55 days of age they were trained to respond on a multiple repeated acquisition (RA) and performance (P) schedule. Each animal went through 80 daily sessions after training was complete. The RA component required the learning of a new three-member sequence of lever pushes each session, and the P component remained constant across sessions. Correct completion of each sequence was rewarded with a food pellet, and mistakes resulted in "time-outs" during which the chamber lights were off and pushing the lever was without consequence. The authors reported that the learning component (i.e., the RA) was selectively affected in the lead-exposed animals in a dose-related manner. The P component was unaffected, indicating that the differences observed in the RA component were not due to a nonspecific effect on the ability to press the lever. The errors committed by the lead-exposed animals in the RA component appeared to be due either to perseverative responding on sequences similar to the P component sequence or perseverative responding on a single lever; both types of behavior prohibited the ability to learn new sequences that were unlike the P component sequence. The possibility that the reduced accuracy in the RA component of the lead-exposed rats was due simply to some sort of impairment in their ability to attend to stimuli indicating the transition from the P to the RA component of a session was eliminated by adding additional stimuli which were without effect. Blood lead levels measured after 60 sessions were 2.8±1.0, 25.1±4.1, and 73.5±5.7 μg/dL for the 0-, 50-, and 250-ppm groups, respectively. No clinical signs of toxicity (if any) or body weight were reported, so it is not possible to ascertain whether these animals exhibited lead toxicity that may have affected the interpretation of the results.

Several studies are available on the effects of postnatal lead exposure on a number of behavioral tests in monkeys. For example, four rhesus monkeys (two male and two female) were exposed to lead as lead acetate trihydrate according to the following regimen: Two doses of 10.0 mg lead/kg were administered to the monkeys on day 8 or 9 and again on day 29 or 30 after birth by nasogastric intubation in distilled water (Levin et al. 1988). From day 9 to day 29 they received 0.7 mg lead/kg/day in their milk formula, and for 12 days after the second dose of 10 mg lead/kg, they received daily doses of 3.0 mg lead/kg/day. For the rest of the first 6 months after birth they were administered 0.7 mg lead/kg/day in the milk formula. Four (two males and two females) rhesus monkeys receiving equiionic doses of sodium acetate served as controls. This treatment regimen was supposed to mimic the temporal pattern of blood levels ("pulse chronic") seen in children. Blood lead levels, ZPP, hematocrit, and body weight were measured. The control monkeys had mean blood levels of 4.1–7.9 μg/dL during the first 6 months. The lead-exposed monkeys had mean blood lead levels of 25.5 μg/dL during the first 4 weeks, which increased to between 33.1 and 42.9 μg/dL during the first 6 months. Blood lead levels peaked at 55.8 μg/dL 5 weeks after birth. The following behavioral tests were conducted in an attempt to identify early predictors of later cognitive impairment resulting from postnatal lead exposure: (1) the early infant behavioral scale (conducted during the first 6 weeks after birth) to screen the development of a broad range of behavioral responses including orientation, muscle tonus, motor maturity, temperament, and quieting abilities; (2) the Piagetian object permanence test (conducted at 14 days of age) to serve as an early measure of cognitive function during the sensorimotor stage of development; and (3) the visual exploration test to assess delayed spatial alternation performance which suggest deficits in visual attention. The lead-exposed infants were more agitated and had lower muscle tonus in the early infant behavior test. All other parameters in this test were not significantly affected by lead exposure. There was also no difference between the lead-exposed monkeys and the controls in the Piagetian object permanence test. Some aspects of the visual exploration test were affected by lead exposure; these changes were suggestive of decreased visual attentiveness in the lead-exposed monkeys. Based on these results, these tests may serve as both indices of behavioral dysfunction during postnatal lead exposure, and to predict later lead-induced cognitive dysfunction (Levin et al. 1988).

Studies of the effects of lead on learning in monkeys are also available. Perinatal exposure to lead nitrate (3 mg lead/kg/day) resulted in significant behavioral deficits in the offspring of Macaca fascicularis at maternal gestational blood lead concentration of 30–70 μg/dL with no signs of maternal toxicity (Hopper et al. 1986). The infant monkeys showed deficits in form discrimination performance (6–18 months age), and in response inhibition performance (19–29 months of age). Persistent deficits in form discrimination up to 18 months following the termination of exposure suggests that lead-induced behavioral deficits may be permanent. Other investigators have used discrimination reversal tasks to detect impaired learning in monkeys treated orally with lead acetate (Bushnell and Bowman 1979b, 1979c; Laughlin et al. 1983; Levin and Bowman 1983; Mele et al. 1984). Discrimination reversal tasks require the subject to correctly respond to one of two stimuli to get a reward and then, once the task has been mastered, to make the reverse discrimination (i.e., respond only to the cue formerly unpaired with reward). In these studies, monkeys administered lead acetate orally from birth at low or high levels (0.2 or 0.88 mg lead/kg/day) that produced blood lead levels of $\geq$32 μg/dL for 5 months to 1 year were consistently slower in reversal and other learning tasks (Bushnell and Bowman 1979a; Laughlin et al. 1983; Levin and Bowman 1989) even when exposure was terminated at 1 year and the monkeys were tested again at 33 months (Mele et al. 1984) and 49–55 months of age (Bushnell and Bowman 1979b). No effects were seen on body weight, growth rate, hematocrit, or general health. The monkeys tested at 49–55 months of age had blood lead levels of 4 μg/dL for controls, 5 μg/dL for the low-lead group, and 6 μg/dL for the high-lead group, as compared with average and peak blood lead levels during the year of treatment of 4 and 12 μg/dL for controls, 32 and 70 μg/dL for the low-lead group, and 65 and 134 μg/dL for the high-lead group (Bushnell and Bowman 1979b, 1979c). Additional evidence was provided by Ferguson and Bowman (1990) in a study on rhesus monkeys where postnatal exposure to varying doses of lead (0.7–10 mg/kg/day) resulted in behavioral alterations such as longer latency to enter the open field and increased activity and retarded habituation while in the open field. These effects were observed 3 years after cessation of exposure although blood levels were similar to controls (≤5 μg/dL); the blood levels averaged 36 μg/dL for the 1st year of age. Although the study was well conducted, it is difficult to determine a dose-response relationship given the unorthodox exposure regimen.

The above findings were supported and extended by other investigators (Gilbert and Rice 1987; Rice 1984, 1985b; Rice and Gilbert 1985; Rice and Willes 1979; Rice et al. 1979). These studies demonstrated impaired learning ability on operant conditioning tasks and discrimination reversal tasks and extended the dose-response observations to lower blood lead levels. Monkeys were given a soluble lead compound orally, 5 days a week, from birth throughout the duration of the studies; doses ranged from 0.05 to 2.0 mg lead/kg/day. Deficiencies in discrimination reversal and/or operant learning were noted in the first 9 months and at 3–4 years with the highest dosage, and at 421 days through 3.5 years at 0.5 mg lead/kg/day (Rice 1984; Rice and Willes 1979; Rice et al. 1979). Peak and steady-state blood lead levels were 115 and 33 μg/dL for the 2.0-mg/kg group and 55.3 and 32.8 μg/dL for the 0.5-mg/kg group. Even at the lowest dosages, 0.05 and 0.1 mg lead/kg/day, the monkeys performed significantly less well in learning discrimination reversals at 3–4 years of age, in learning a delayed alternation task at 6–7 years of age, and in learning discrimination reversals in the presence of irrelevant cues at 9–10 years of age (Gilbert and Rice 1987; Rice 1985b). In this series of studies on the same monkeys, peak and steady-state blood lead levels were 15 and 11 μg/dL, respectively, for the 0.05-mg/kg group and 25 and 13 μg/dL, respectively, for the 0.1-mg/kg group (Gilbert and Rice 1987; Rice 1985b).

In addition to the confirmation of the observation that lead-treated monkeys were impaired in their ability to learn discrimination reversal tasks, notable findings were the tendency of lead-treated monkeys to respond excessively or inappropriately (e.g., with more responses than controls during time-outs) in operant schedules when responses were not rewarded (Rice et al. 1979). In addition, lead-treated monkeys were also slower to learn reinforcement schedules which required a low rate of responding (Rice and Gilbert 1985), tended to have higher response rates and shorter inter-response times on fixed-interval operant schedules, and made more perserverative errors on operant matching-to-sample tasks which required them to direct their responses according to stimulus colors (Rice 1984). These characteristic findings are similar to those seen in rats as discussed previously. No overt signs of toxicity were observed in the monkeys.

Simple visual reaction time has proven not to be as sensitive an indicator of lead-induced neurotoxicity as some of the other behavior paradigms discussed above. Adult monkeys were tested in a simple visual reactive time task (Rice 1988). Seven cynomolgus monkeys (three female controls and two lead-treated monkeys of each sex) were used in this study. The lead-treated monkeys received 0.5 mg/kg/day of lead from birth into adulthood. The exact mode of administration was not specified. This study was conducted when the monkeys were approximately 7 years of age. Blood lead levels increased from birth to 53 μg/dL by 100 days of age, were stable at this level until 200 days of age, and then restabilized at a concentration of 33 μg/dL. The monkeys were trained to perform a simple visual reaction time task using delays between 1 and 13 seconds. There were no differences in performance between the control and treated monkeys. Based on these results the authors concluded that this simple paradigm used to measure reaction time was not a sensitive indicator of lead toxicity. These authors had previously demonstrated performance deficits in the same group of monkeys using different behavioral tasks.

Electrophysiological studies have reported effects at higher blood lead levels than have the neurobehavioral studies presented above. Suckling rats whose dams were given 152.9 mg lead/kg/day as lead acetate in their drinking water had significant alterations in the visual evoked responses (VERs) and decreased scotopic visual acuity at postnatal day 21, at which time their blood lead levels averaged 65 μg/dL (Fox et al. 1977). Effects on the nervous system were persistent; decreases in visual acuity and spatial resolution were observed at 90 days of age in rats exposed only from birth to weaning as noted above (Fox et al. 1982). Further investigations by this laboratory on the effects of pre- and postnatal exposure of rats to lead on the eye are discussed in Section 2.2.3.2.

Similarly, NCV changes have also been used as indicators of lead-induced neurotoxicity (see Section 2.2.1.4), and these effects also occur at higher blood lead levels than those at which neurobehavioral effects are observed. The effects of lead exposure on motor NCV were evaluated in rats administered lead acetate in the drinking water for 15 weeks at the following doses: 0, 89.6, 448, 896, and 1,792 mg lead/kg/day (Yokoyama and Araki 1986). Body weight, blood lead levels, and nerve lead levels were measured at the termination of the exposure period. Maximal motor NCV of the left sciatic nerve was measured in ether anesthetized rats after 15 weeks of exposure to lead. NCV was significantly decreased in the 89.6 mg lead/kg/day group as compared to the controls (46.8 meters/second versus 51.2 meters/second). This decrease was roughly dose-dependent, although a wide range of NCVs were observed at each dose. NCV was significantly correlated with blood lead levels in all treated groups, but did not correlate with nerve lead levels or body weight. The authors concluded that blood lead level is a better indicator of the effect of lead on NCV because it reflects the "active" lead in the peripheral nerves, whereas the nerve lead level may represent an "inactive" form of lead.

The highest NOAEL values and all reliable LOAEL values for each study for neurological effects are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.3.5 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to inorganic lead. See Section 2.2.1.5 for a discussion of developmental effects in humans after multi-route exposure to lead.

Twenty-three teratogenicity studies in which lead compounds (acetate or nitrate) were administered in the drinking water or feed or by gavage to rats and mice have shown no evidence that lead causes malformations, but some evidence that lead causes fetotoxic effects. The following discussion is based on the teratogenicity studies most relevant to current concerns for human prenatal exposure along with studies concerned primarily or exclusively with the neurobehavioral effects of prenatal exposure to lead.

In rodents, a greater proportion of nervous system development takes place postnatally than in humans. Accordingly, rodent studies of developmental neurobehavioral toxicity that extend exposure into the early postnatal period are probably more analogous to human prenatal exposure than are rodent studies that use only prenatal exposure.

Following oral administration of lead acetate at doses up to 64 mg lead/kg/day to rats before breeding and throughout pregnancy, the only effect seen was fetal stunting at the high dose (Miller et al. 1982). However, the lack of effect on fetal brain and litter size indicated that lead exposure failed to influence development in rats. Maternal blood lead values ranged from 80 to 92 μg/dL prior to mating and from 53 to 92 μg/dL during pregnancy. Pretreatment and control blood lead levels averaged 6–10 μg/dL. Similar results were obtained in rats administered up to 390 mg/kg/day by gavage on gestations days 6–16. Fetotoxicity (retarded skeletal development) was evident at the high dose, a dose that was maternally toxic as well (Kennedy et al. 1975), In a later study, Rabe et al. (1985) exposed female rats to lead acetate at 448 mg lead/kg/day in the drinking water prior to mating and throughout gestation. The pups were transferred to unexposed foster dams on the 2nd day after birth. Mean blood lead levels were 98 μg/dL at day 1 and 20 μg/dL at day 16 of age in pups from treated dams and approximately 10 μg/dL at both ages in pups from control dams. Body weights were reduced in treated pups relative to controls at birth but not at 30 days of age. Neurobehavioral function (surface righting and negative geotaxis reflexes, spatial discrimination, and reversal in T-maze), tested in the pups at 17 days of age, was not affected by prenatal lead treatment. In a study conducted on Binghamton Heterogeneous Stock mice by Draski et al. (1989), dams received lead acetate (608 mg lead/kg/day) in their drinking water during gestation; at birth, litters were cross-fostered so as to receive postnatal exposure to lead acetate. The blood lead level in treated dams was 100 μg/dL (versus <10 μg/dL in controls); in pups the levels ranged from 76 to 130 μg/dL (versus 3–6 μg/dL in controls) during postnatal days 5-15. The open field test and time to return to home cage showed changes in behavioral patterns of pups depending on the developmental stage during which the dams were exposed, as well as age and conditions when tested. However, because of the use of single-dose level in these studies, the dose-response relationship could not be evaluated.

The different aspects of a study of prenatal, postnatal, and long-term exposure of rats to lead were presented by Kimmel et al. (1980) and Grant et al. (1980). The well-conducted study by Kimmel et al. (1980) provided a variety of relevant dose-effect data. In this study, female rats were exposed to lead acetate in the drinking water at 0.07, 0.7, 3.5, 7, and 35 mg lead/kg/day from weaning through mating, gestation, and lactation. The pups were weaned onto the same drinking water solutions as their dams received. In addition, some of the dams were killed at day 21 or 22 of gestation for evaluation of the fetuses and uteri. Toxicity to the dams (dose-related slight depression of body weight and delay in time of vaginal opening) was seen at ≥3.5 mg/kg/day. Exposure to lead did not affect the ability of females to conceive, to carry a normal litter to term, or to deliver offspring. No significant differences in indices of embryo- or fetotoxicity or teratogenicity were seen in treated groups relative to controls. Length of gestation and birth weights were unaffected, but mean crown-rump length of 1-day-old female pups in the 35-mg/kg/day group was significantly shorter than in controls. Median blood lead levels just prior to mating and at day 21 of gestation were 1 and 4 μg/dL for controls, 9 and 12 μg/dL for the 0.7-mg/kg/day group, 20 and 23 μg/dL for the 3.5-mg/kg/day group, 24 and 35 μg/dL for the 7-mg/kg/day group, and not reported for the 35-mg/kg/day group (Kimmel et al. 1980).

Significant delays in vaginal opening in female pups of groups receiving ≥3.5 mg lead/kg/day and significant delays in the development of surface and air righting reflexes in pups receiving 7 or 35 mg lead/kg/day were reported by Grant et al. (1980). Blood lead levels of the pups at 1 and 11 days were 4 and 3 μg/dL for controls, 37 and 22 μg/dL for 3.5-mg/kg/day pups, 57 and 35 μg/dL for 7-mg/kg/day pups, and not reported for 35-mg/kg/day pups. In comparing the results of this study with results of the study by Rabe et al. (1985), in which no effects on the development of reflexes were seen at a much higher level of lead in the drinking water, it should be noted that exposure to lead in the Rabe et al. (1985) study ceased shortly after birth, but in the Grant et al. (1980) study exposure to lead continued through the time of testing.

Delays in the development of the righting reflex were observed by Reiter et al. (1975) in rat pups whose dams were exposed to lead acetate at concentrations of 0.7 and 7 mg lead/kg/day in their drinking water throughout gestation and lactation. Eye opening was delayed at the higher exposure level. Blood lead levels were not determined.

In assessing the behavioral responses of rat pups, Taylor et al. (1982) found that exposure of female rats, prior to mating and through gestation and lactation, to lead acetate (28 and 56 mg lead/kg/day) in the drinking water did not result in significant differences in the pups' acquisition of a response when tested at 11 days of age, but did result in significantly slower extinguishing of the response when the reward was no longer provided. Blood lead levels at 21 days of age were 3.7 μg/dL in controls, 38.2 μg/dL in the low-exposure group, and 49.9 μg/dL in the high-exposure group.

Neurobehavioral effects in infant monkeys were examined by Levin and Bowman (1983) who treated adult female monkeys orally with lead acetate at 1.9 and 3.8 mg lead/kg/day prior to mating and throughout gestation. Blood lead levels at birth were 5, 30, and 55 μg/dL in control (n=5), low-lead (n=3), and high-lead (n=4) groups, respectively. Treatment of the mothers produced no changes in early social behavior of their infants and no differences in learning ability, relative to controls, when the offspring were tested on a search task at 4–5 years of age. However, the dosing was administered over variable dose ranges throughout the study, which indicates metabolic differences in maintaining the blood lead levels.

Histological changes have been reported in the brains of rat pups at much higher blood lead levels than those reported above. Administration of lead chloride (28 mg lead/kg/day) in drinking water to pregnant rats during gestation and lactation was reported to produce a less mature synaptic profile in the cerebral cortex of the pups at postnatal day 15 (McCauley et al. 1979) and a 30% reduction in synaptic density in the cerebral cortex at postnatal day 15 but not day 21 (McCauley et al. 1982). Blood lead levels were 80 μg/dL at birth. Although the authors reported a dose-dependent increase in blood lead levels in pups from the 4.2 and 28 mg/kg/day groups, the synaptic counts were measured only for pups from the high-dose group.

Decreased numbers of dendritic spines and malformed spines in brain parietal cortex were observed at postnatal day 30 in rat pups whose mothers were administered 256–480 mg lead/kg/day as lead acetate in drinking water during gestation and lactation (Murray et al. 1978). Blood lead levels were not reported.

Gestational exposure of guinea pigs to 5.5 or 11 mg lead/kg/day produced dose-dependent alterations of neuroglial enzymes (glutamine synthetase and glycerol-3-phosphate dehydrogenase) and changes in trace metal levels (Sierra et al. 1989). The blood levels in dams and fetuses associated with these changes were within the range of 10–30 μg/dL lead. However, the authors did not examine for histopathological alterations in neural tissue.

Some studies have investigated the effects of prenatal exposure to lead on heme metabolism. Hubermont et al. (1976) administered lead nitrate at concentrations of 0.009, 0.09, and 0.9 mg lead/kg/day in drinking water to female rats before mating, throughout gestation, and during lactation. Blood lead levels in the dams and pups that received 0.9 mg lead/kg/day group were 68 and 42 μg/dL, respectively. An increase in free tissue porphyrins and a decrease in blood ALAD activity were seen in the pups that received 0.9 mg lead/kg/day, as compared with controls. The study did not examine the long-term hematological effects of lead.

Effects at even lower external and internal exposure levels were reported by Hayashi (1983). Lead acetate at 0.7 mg lead/kg/day in the drinking water of rats for the first 18 or 21 days of pregnancy resulted in decreased ALAD activity in the fetal and maternal erythrocytes and increased ALAD activity in fetal but not maternal liver. Fetal, but not maternal, hematocrits and hemoglobin levels were decreased in the group treated for 21 days. Fetal blood lead levels were 27 μg/dL and 19 μg/dL in the 18-day and the 21-day treated groups, respectively. Maternal blood lead levels were approximately 4 μg/dL in treated and control groups. The study is limited by the use of one dose level, which precluded assessment of dose response.

Limited data are available for lead-induced renal toxicity in animals (Fowler et al. 1980); however, it does not appear to be a sensitive end point for lead toxicity in humans. Also, immune deficiencies have not been observed in immune function studies in humans (adults and children) at blood lead levels higher than those that produced changes in the immune systems of rats (Blakley et al. 1980; Faith et al. 1979; Luster et al. 1978). These studies are discussed in more detail in Sections 2.2.3.2 and 2.2.3.3.

The highest NOAEL values and all reliable LOAEL values for each study for developmental effects are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.3.6 Reproductive Effects

According to EPA (1986a), lead was used in preparations sold as abortifacients in Britain around the turn of the century. These preparations were apparently effective at levels that produced marked signs of lead poisoning in the women. The available studies were methodologically inadequate and did not provide dose-effect information. Evidence for adverse reproductive outcomes in women with obvious lead poisoning is of little help in defining the effects of lead at much lower exposure levels.

An adverse effect of lead on pregnancy rate has been noted in animal studies (Kennedy et al. 1975). Acute-duration gavage administration of 390 mg lead/kg/day as lead acetate to rats resulted in a sharp decrease in pregnancy rates. This effect was not noted at 39 mg lead/kg/day. The study limitations include a lack of measurement of blood lead levels and lack of statistical analysis of pregnancy incidence. A decrease in the number of implantations was noted in untreated female mice that were mated to males that had been treated with 141 mg/kg/day lead chloride in the drinking water for 3 months (Johansson and Wide 1986).

No treatment-related effects on reproductive indices were noted in rats exposed to up to 0.9 mg lead/kg/day as lead nitrate in the drinking water 3 weeks before mating, during gestation, and during lactation (Hubermont et al. 1976). However, other animal studies have reported lead-induced damage to the ovaries and testes. Such effects of lead were examined by Hilderbrand et al. (1973) who reported that oral dosing with low dose levels of lead acetate, 0.014 and 0.26 mg lead/kg/day for 30 days, produced higher blood lead levels (than in the study by Grant et al. [1980]) of 30 and 53 μg/dL, respectively. Irregular estrous cycles occurred at both treatment levels, and ovarian follicular cysts with reductions in numbers of corpora lutea occurred at the higher level. Male rats treated orally with lead acetate (0.013 and 0.26 mg lead/kg/day) in the same manner had blood lead levels of 19 and 30 μg/dL, respectively, and had testicular damage at the higher exposure level, with increased prostate weight at the lower level. No details regarding the strain of rats used were provided. Use of an additional dose level would have allowed assessment of dose-response.

In a later study of lead effects on male reproductive tract, Chowdhury et al. (1984) found testicular atrophy and cellular degeneration in male rats given lead acetate in drinking water at 90 mg lead/kg/day for 60 days. Blood lead levels averaged 142.6 μg/dL. At a lower exposure level of 45 mg lead/kg/day and mean blood lead level of 71.7 μg/dL, the seminiferous tubular diameter and spermatic count were reduced. No significant changes were seen at 22 mg lead/kg/day and a blood lead level of 54.0 μg/dL. The study is limited by the lack of determination of whether the partial inhibition of spermatogenesis observed at 45 mg lead/kg/day was a transitional effect.

Decreases in sperm motility and increased acid phosphatase activity were reported to result from oral administration of 0.05 mg/kg lead in drinking water to male rats for 20–30 days in a study from the former

U.S.S.R. (Krasovskii et al. 1979). Dystrophic changes of the Leydig cells were reported in gonadal tissues of rats exposed to doses as low as 0.005 mg lead/kg/day. The weaknesses of the study include absence of data on the strain and number of rats used, and the blood lead levels were not reported.

Male rats exposed to lead acetate in drinking water through the dams during gestation and lactation and then directly until 9 months of age exhibited no significant effects on sperm count or sperm morphology (Fowler et al. 1980). The blood lead levels in these animals ranged from 4.5 to 67 μg/dL. Rats administered 0.19 mg lead/kg/day as lead acetate by gavage for 9 weeks exhibited a significant reduction in the number of spermatozoa within the cauda epididymis. At 192 mg lead/kg/day, the number of abnormal spermatozoa increased significantly, but a decrease in the number of spermatozoa was not significant. No adverse effects were noted in the testes. The results of this study indicate that lead affected spermatozoa after release from the germinal epithelium which was possibly protected from the effects of lead by the blood-testes barrier (Barratt et al. 1989).

Pre- and postnatal exposure of female animals to lead can affect pubertal progression and hypothalamic-pituitary-ovarian-uterine functions in offspring. The administration of lead acetate in drinking water to rats, both indirectly through the dams during gestation and lactation and then directly, produced no effects on female offspring exposed to 0.7 mg lead/kg/day but delayed the vaginal opening in females exposed to ≥3.5 mg lead/kg/day (Grant et al. 1980); these females were not retarded in their growth. Similar effects were also reported in dams receiving lead acetate prior to breeding (Kimmel et al. 1980). This effect was dose-dependent.

An effect of lead on central regulation of endocrine functions through the hypothalamus-pituitary axis has also been observed in adult animals. Following exposure to 40 mg lead/kg/day administered as lead acetate in drinking water, histopathological examination of the gonads and thyroid gland and measurements of serum testosterone, 17ß-estradiol, follicle stimulating hormone (FSH), LH, prolactin, TSH, T_3, and T_4 were conducted. No changes were seen at the 40- and 81-mg/kg/day dose levels. No lead uptake was noted in the gonads. However, the lowest dose was sufficient to reduce serum prolactin and LH levels significantly (Sourgens et al. 1987).

The highest NOAEL for reproductive effects in rats and mice and all reliable LOAELs for reproductive effects in rats, mice, and monkeys are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.3.7 Genotoxic Effects

Eleven male volunteers aged 20-30 years ingested lead acetate for 49 days. Blood lead levels were kept at approximately 40 μg/dL. The frequency of chromosome aberrations was assayed after lymphocyte culture for 72 hours and found to be no different from that of 10 controls. The lead-exposed subjects did show a higher mitotic activity (Bulsma and DeFrance 1976).

Intermediate-duration exposures of mice to lead in the diet resulted in slight increases in chromatid gaps, but no significant increases in any class of serious chromosome aberration (Jacquet et al. 1977). Cytogenetic analysis was performed on bone marrow cells of Wistar rats exposed to 500 ppm lead acetate in drinking water for 6 weeks. Although there was a marked increase in chromosome pulverization and erosion, there was no increase in the frequency of chromosomal aberrations. Sister chromatid exchanges were slightly, but significantly, increased over controls (Kowalska-Wochna et al. 1988).

Monkeys given daily doses of 1 or 5 mg of lead by intubation for 12 months showed only minor chromosome aberrations such as chromatid and chromosome gaps and fragments at the beginning of the experiment. After 7 months of exposure, more severe aberrations (translocations and dicentrics) appeared in the lymphocytes. However, no statistically significant difference in severe aberrations between the exposed monkeys and the controls was ever seen. Lead treatment did produce a significant increase in the number of gaps, but this was not related to dose or to measured blood lead level (Jacquet and Tachon 1981). An earlier chronic study on monkeys given lead acetate in the diet 6 days a week for 16 months showed that severe chromosome abnormalities occurred only in animals given a calcium-deficient diet (Deknudt et al. 1977).

Other genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer in humans after oral exposure to inorganic lead. See Section 2.2.1.8 for a discussion of cancer in humans following multi-route exposure to lead.

The available data on the carcinogenicity of lead following ingestion by laboratory animals indicate that lead acetate and lead phosphate are carcinogenic, and that the most common tumor response is renal tumors. However, the extremely high cumulative doses of lead used in these studies are difficult to extrapolate to low-level exposure in humans, and thus do not provide a sufficient basis for quantitative risk assessment (see Section 2.4). In addition, it is possible that the high doses required to induce renal tumors may themselves have produced a carcinogenic effect that was independent of any direct effect of lead as a result of nonspecific tissue damage. Furthermore, the relevance of male rat kidney tumors induced by some chemicals to humans has been questioned (EPA 1991c). It is not known whether the mechanism by which lead induces tumors in the rat kidney involves the same or similar species-specific proteins (α_{2u}-globulin) identified in the recent studies of other substances, such as unleaded gasoline (see Section 2.9.3 for a discussion of ongoing research designed to answer this question). Other deficiencies associated with these animal studies that limit their usefulness with respect to risk assessment include the fact that they are generally over 10 years old with small group sizes and poor reporting of results.

The most comprehensive set of studies was performed by Azar et al. (1973), who administered lead acetate to rats for 2 years. Renal tumors occurred in 5 of 50 male rats that received 27 mg lead/kg/day, in 10 of 20 males that received 56.5 mg lead/kg/day, and in 16 of 20 males and 7 of 20 females that received 105 mg lead/kg/day. No renal tumors were observed in the control groups or in rats administered 0.9–7 mg lead/kg/day. Limitations associated with this study include the following: experimental details were not reported, the likelihood of environmental contamination from lead in the air or drinking water was not mentioned, and the strains of rats used were not specified. Body weight gain in the two highest dose treatment groups was reported to be depressed, but no details were given regarding this finding.

Male Sprague-Dawley rats were administered lead acetate equivalent to 37 mg lead/kg/day in their drinking water for 76 weeks as part of a study to determine interactions between sodium nitrite, ethyl urea, and lead. There were no kidney tumors in the 10 control rats. Renal tubular carcinomas were found in 13 (81%) of the 16 treated rats. Three of these tumors were detected at 72 weeks and the remaining were found at terminal necropsy (Koller et al. 1985).

An increased incidence of renal tumors (7 out of 25 combined adenomas and carcinomas) was observed in male Swiss mice fed 0.1% basic lead acetate in the diet for 2 years (Van Esch and Kroes 1969). No renal tumors were found in the control animals. One female in the 1.0% treatment group had a renal tumor. The authors attributed the low tumor incidence in the 1.0% group to early mortality.

The cancer effects levels described above are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.4 Dermal Exposure

No studies were located regarding the following effects in humans or animals after dermal exposure to inorganic lead. See Section 2.2.1 for a discussion of these effects in humans following multi-route exposure to lead:

2.2.4.1 Death
2.2.4.2 Systemic Effects
2.2.4.3 Immunological Effects
2.2.4.4 Neurological Effects
2.2.4.5 Developmental Effects
2.2.4.6 Reproductive Effects
2.2.4.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.4.8 Cancer

No adequate studies were located regarding cancer in humans or animals after dermal exposure to inorganic lead. See Section 2.2.1.8 for a discussion of cancer in humans following multi-route exposure to lead.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Inorganic Lead. Prior to the actual absorption of lead by the lungs, some fraction of inhaled airborne lead must be deposited in the respiratory tract. The rate of deposition of particulate airborne lead in adult humans is approximately 30–50% and is modified by factors such as particle size and ventilation rate (EPA 1986a). Once deposited in the lower respiratory tract, particulate lead is almost completely absorbed, and all chemical forms of lead also appear to be absorbed (EPA 1986a; Morrow et al. 1980). After subjects breathed lead chloride, with a mass median aerodynamic diameter (MMAD) of 0.26 μm, and lead hydroxide, with an MMAD of 0.24 μm, through a standard respiratory mouthpiece for 5 minutes, 23% and 26%, respectively, of the aerosol was deposited in the lungs and respiratory tract (Morrow et al. 1980).

Absorption is suggested by elevated blood lead concentrations in subjects who were continuously (23 hours per day) exposed to 0.0032–0.011 mg lead/m^3 for 18 weeks (the species of lead to which the subjects were exposed was not specified) (Griffin et al. 1975b). Elevated blood and urinary lead concentrations were also found in volunteers exposed to 0.15 mg lead/m^3 for 7.5 hours per day, 5 days per week for 16–112 weeks (Kehoe 1987). Blood lead concentrations as high as 45 μg/dL were observed in one subject exposed at that rate for 2 years. Daily lead absorption of 14 μg was reported for five male volunteers who inhaled ambient air (0.002 mg lead/m^3) (Rabinowitz et al. 1977). Some evidence for complete absorption of lead from the respiratory tract may be the lack of lead found at autopsy in the lung tissues of occupationally exposed lead workers (Barry 1975) and nonoccupationally exposed subjects (Gross et al. 1975).

Organic Lead. Following a single exposure to vapors of tetraalkyl lead compounds (approximately 1 mg/m^3 breathed through a mouthpiece, 10–40 breaths of approximately 1 L volume) in four male subjects, 37% and 51% of inhaled tetraethyl and tetramethyl lead, respectively, were initially found in the respiratory tract, but a considerable percentage of these volatile compounds was lost through exhalation (Heard et al. 1979). Approximately 60–80% of the deposited tetraalkyl lead was absorbed by the lungs. In a case report of a 22-year-old male exposed to tetramethyl lead, absorption was evident because of elevated urinary lead levels for 4 days after exposure (Gething 1975).

Limited experimental data suggest that inhaled lead is absorbed rapidly by animals (EPA 1986a). One hour after female Wistar rats breathed total lead concentrations of 0.01 mg lead/m^3 as tetraethyl lead in the form of aerosolized leaded gasoline labeled with lead-210 (^{210}Pb) tracer for 30–45 minutes, lead clearance in the lungs was 30%; the majority of the particles were 0.1–0.5 μm in diameter (Boudene et al. 1977). Immediately after nose-only breathing of engine exhaust aerosols containing 6 mg lead/m^3 as lead-203 (^{203}Pb)-labeled tetraethyl lead for 40 or 60 minutes, 25% of the dose was accounted for in tissues other than the lung and gastrointestinal tract in rats (Morgan and Holmes 1978). Initially, the lead content in lungs decreased quite rapidly; only 7.5% of the dose was retained in the lungs after 48 hours, followed by a slower decline in which less than 2% of the dose remained in the lungs after a week. The lung had the lowest tissue lead content in rats and rhesus monkeys who inhaled 0.0215 mg lead/m^3 continuously (22 hours per day) for a year (Griffin et al. 1975b).

2.3.1.2 Oral Exposure

Although there were limited data, oral absorption of lead appears to be low in humans, except in children. The extent and rate of gastrointestinal absorption are affected by fasting and the solubility of a particular lead salt in gastric acid. Male subjects were fed diets supplemented with 0.0008–0.003 mg/kg/day of lead-204 (^{204}Pb)-labeled lead nitrate for up to 124 days in which 6.5–10.9% of the tracer was absorbed (Rabinowitz et al. 1976). Absorption can be as high as 45% in adults under fasting conditions to as low as 6% with food (Chamberlain et al. 1978). It was reported that intestinal absorption of lead chloride was 3% with meals but increased to 60% when the subjects were fasted (Heard and Chamberlain 1982). Interindividual variability of oral absorption is shown in the study by Heusler-Bitschy et al. (1988) in which intestinal absorption ranged from 10% to 80% in eight fasted volunteers receiving a single exposure of 0.007 or 0.02 mg lead/kg/day in drinking water.

There is indirect evidence from autopsies which reveal high lead content in tissues, occurring from life-time exposure (Barry 1975). Oral intake of lead can result from consuming lead-containing food and beverages and from swallowing lead deposited in the upper respiratory tract after inhalation exposure (Kehoe 1987). In addition, the ingestion of lead in children may occur through normal mouthing activity and pica, which is the ingestion of material not fit for food, such as soil, clay, ashes, paint chips, or plaster (EPA 1986a). The primary site of lead absorption in children is the gastrointestinal tract (Hammond 1982). For dietary lead, absorption in children is approximately 50% compared with 15% gastrointestinal lead absorption measured in adults (Chamberlain et al. 1978). When daily intake was greater than 0.005 mg lead/kg, absorption was increased from 26.2% to 41.5% in infants, 2 weeks to 2 years of age, who were exposed for 72 hours to lead in milk and commercially prepared strained food (Ziegler et al. 1978). However, the authors indicated that at lower lead levels there was difficulty in controlling lead intake.

There is evidence to suggest that gastrointestinal absorption in animals is controlled by a saturation phenomenon, as well as influenced by fasting (Aungst et al. 1981). In fasted rats, absorption was estimated at 42% and 2% following single oral administration of 1 and 100 mg lead/kg, respectively, as lead acetate (Aungst et al. 1981). In mice, absorption was 14% in fasted mice versus 7.5% in fed mice 4 hours following an oral gavage dose of 0.003 mg lead/kg as lead acetate (Garber and Wei 1974). However, no difference in absorption (4–5%) was observed in fasted and nonfasted mice receiving 2 mg lead/kg.

The extent of gastrointestinal absorption of lead in experimental animals is age dependent. The rat pup absorbs 40–50 times more lead via the diet than does the adult rat (Forbes and Reina 1972; Kostial et al. 1978). In rats receiving an oral dose of 1 mL lead-212 (^{212}Pb)-labeled tracer, absorption was approximately 74–89% for animals 16–22 days of age, 15–42% in animals 24–32 days old, and only 16% at 89 days old (Forbes and Reina 1972). A single dose of lead resulted in 52% absorption in 1-2-week-old suckling rats compared to 0.4% in adults (Kostial et al. 1978). Age differences in absorption rate were evident in rat pups who had slightly higher tissue levels compared to adult rats following a single gavage dose of 1 or 10 mg lead/kg as lead acetate (Aungst et al. 1981). Absorption was 37.9% for young monkeys versus 26.4% in adults following a single radiolabeled gavage dose of 6.37 mg lead/kg as lead acetate (Pounds et al. 1978). This age difference may be due, in part, to dietary differences and to the presence of an undeveloped, selective intestinal barrier to lead in the rat neonate (EPA 1986a).

Particle size also influences the degree of gastrointestinal absorption (EPA 1986a; Grobler et al. 1988). An inverse relationship was found between diets containing metallic lead of particle sizes ≤250 μm and absorption in rats (Barltrop and Meek 1979). There was a 2.3-fold increase in tissue lead concentration when animals ingested an acute dose of 37.5 mg/kg with a particle size of <38 μm (diameter) compared to a particle diameter of 150–250 μm (Barltrop and Meek 1979).

2.3.1.3 Dermal Exposure

Inorganic Lead. Limited information is available regarding absorption after dermal exposure in humans. Dermal absorption of inorganic lead compounds is reported to be much less significant than absorption by inhalation or oral routes of exposure, because of the greatly reduced dermal absorption rate (EPA 1986a). Following skin application of ^{203}Pb-labeled lead acetate in cosmetic preparations (0.1 mL of a lotion containing 6 mmol lead acetate/L or 0.1 g of a cream containing 9 mmol lead acetate/kg) to eight male volunteers for 12 hours, absorption was ≤0.3%, but expected to be 0.06% during normal use of such preparations (Moore et al. 1980). Most of the absorption took place by 12 hours of exposure.

Organic Lead. No studies were located regarding dermal absorption of inorganic lead in animals; however, tetraalkyl lead compounds have been shown to be rapidly and extensively absorbed through the skin of rabbits and rats (Kehoe and Thamann 1931; Laug and Kunze 1948). A 0.75-mL amount of tetraethyl lead, which was allowed to spread uniformly over an area of 25 cm^2 on the abdominal skin of rabbits, resulted in 10.6 mg of lead in the carcass at 0.5 hours and 4.41 mg at 6 hours (Kehoe and Thamann 1931). Tetraethyl lead was reported to be absorbed by the skin of rats to a much greater extent than lead acetate, lead oleate, and lead arsenate (Laug and Kunze 1948).

2.3.2 Distribution

Inorganic Lead. Once absorbed, inorganic lead is distributed in essentially the same manner regardless of the route of absorption (Kehoe 1987). This implies that a common lead transport system is involved. Therefore, the distribution and body burden of absorbed lead for all routes will be discussed in one section.

The body burden of a particular chemical is the total amount of that chemical found in the body. The distribution of lead in the body is initially dependent on the rate of delivery by the bloodstream to various organs and tissues. A subsequent redistribution may then occur, based on the relative affinity of tissues for the element and its toxicodynamics there (EPA 1986a). With consistent exposure for an extended period, a steady state of intercompartmental distribution is achieved; however, fluctuation can occur when short-term exposure is superimposed on the long-term uptake pattern (EPA 1986a).

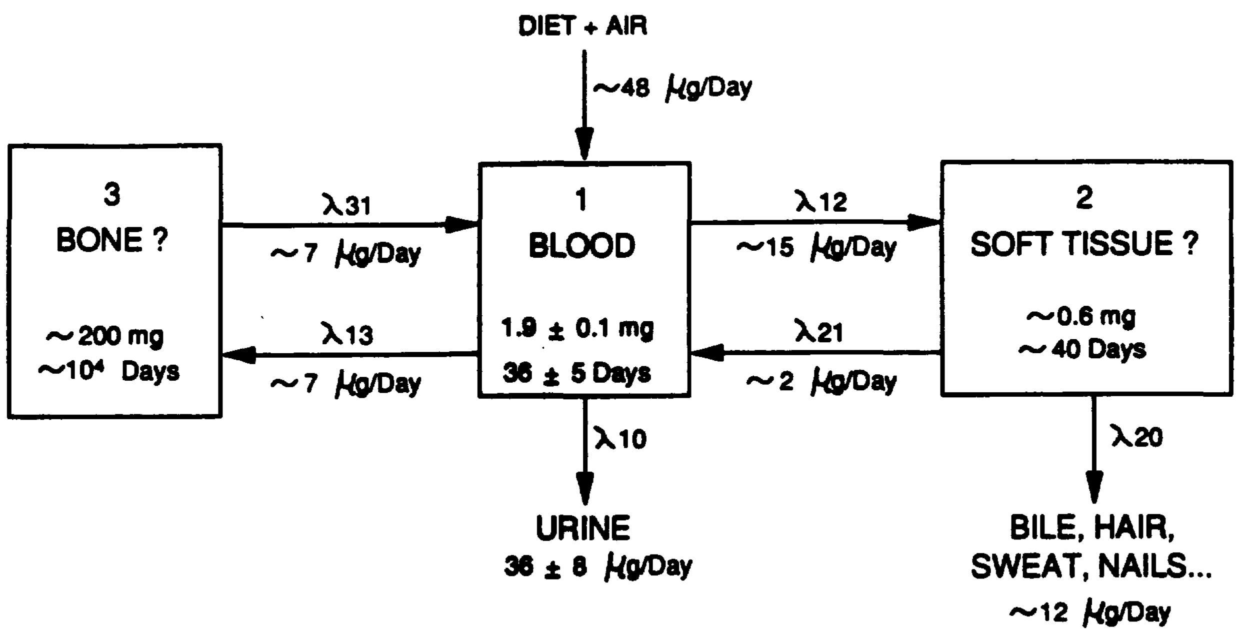
The distribution of lead in humans has been well characterized. It is carried primarily in the red blood cell (99%) rather than the plasma (DeSilva 1981; EPA 1986a; Everson and Patterson 1980). Most of the lead found in red blood cells is found bound within the cell rather than the erythrocyte membrane. Within the cell, 50% of lead is bound to hemoglobin A_2 (EPA 1986a). Another 5% is bound to a 10,000-dalton molecular-weight fraction, approximately 20% to a much heavier molecule, and about 25% is considered "free" or bound to lower weight molecules (EPA 1986a; Raghavan and Gonick 1977). Fetal hemoglobin appears to have a higher affinity for lead than adult hemoglobin (Ong and Lee 1980).

Rather than being distributed homogeneously throughout the body, lead is dispersed among several physiologically distinct compartments. Recently, a software application for a lead uptake/biokinetic model was developed in which uptake is estimated by daily intake from air, water, and soil to calculate the amount of lead in different body compartments (EPA 1990d). In addition, a number of mathematical pharmacokinetic models for lead have been proposed to explain and predict such parameters as intercompartmental lead exchange rates, retention of lead in various pools, and relative rates of distribution among the tissue groups. A three-compartment model proposed by Rabinowitz et al. (1976), based on tracer and balance data from five healthy men, identifies the relative proportioning of lead between the bone, blood, and soft-tissue pools (Figure 2-3). The figure shows the lead content and mean half-life of each pool and the rates of lead movement between pools (λ). The blood compartment shows the shortest half-life (36 days), followed by the soft-tissue compartment (40 days), and then by the bone compartment (10^4 days or approximately 27 years). Bone contains most of the total body burden of lead. Further refinement of this three-compartment model is advanced by Marcus (1985a, 1985b, 1985c) and presented in Figure 2-4.

The generation of more recent data on lead pharmacokinetics has allowed for a refinement of this three-compartment model. A multicompartment kinetic model for lead was proposed which addresses the diffusion of lead into bone and such principles as plasma-erythrocyte lead interactions (Marcus 1985a, 1985b, 1985c). For the bone diffusion model, Marcus (1985a) used the lead kinetic parameters generated for the dog. This model, which accounts for the exchange of lead between blood in bone canaliculi and the crystalline bone of the osteon, enables one to predict the effect of a number of parameters (such as diffusion and surface area) on the kinetics of lead in bone. A similar multicompartment model was developed by Marcus (1985c) to describe the kinetics of lead in plasma and erythrocytes. Based on the data collected by DeSilva (1981), Marcus (1985c) incorporated four blood lead compartments into his model: diffusible lead in plasma, protein-bound lead in plasma, a "shallow" erythrocyte pool, and a "deep" erythrocyte pool. This relationship is depicted in Figure 2-4. When this model is applied to the data of DeSilva (1981), a curvilinear relationship results between plasma and blood lead levels.

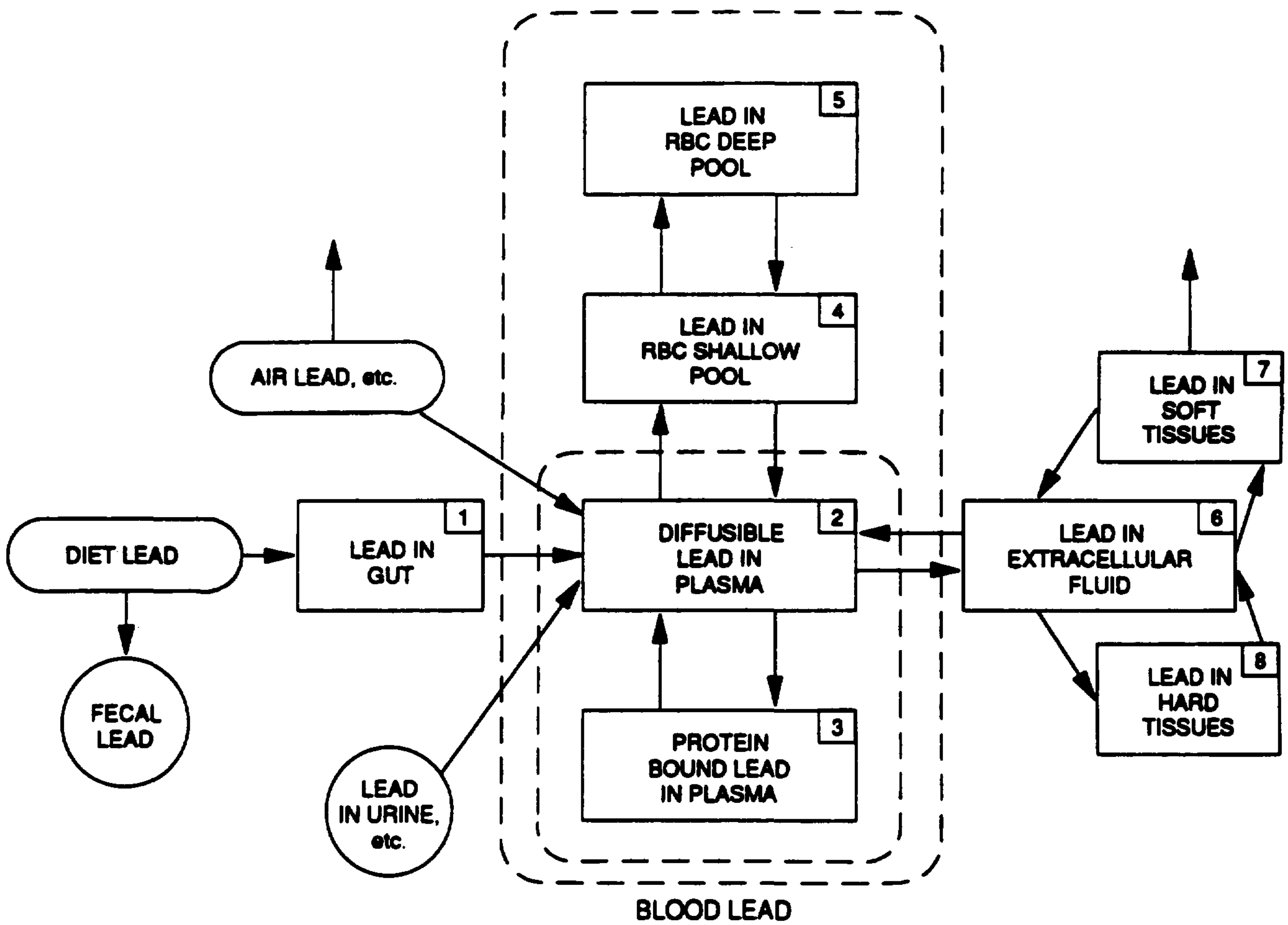
In adult volunteers exposed to 0.0032–0.011 mg lead/m^3 (species of lead not specified) continuously for 18 weeks, blood lead levels increased for about 12 weeks then leveled off between 27 and 37 μg/dL (Griffin et al. 1975b). Lead content in blood declined after cessation of exposure, returning to pre-exposure levels by 5 months. The half-life of lead in adult human blood has been measured as 36 days by Rabinowitz et al. (1976) and 28 days by Griffin et al. (1975b). Under steady-state conditions, 96%–99% of blood lead

FIGURE 2-3. Lead Metabolism Model*



* Derived from Rabinowitz et al. 1976

FIGURE 2-4. A Compartmental Model for Lead Biokinetics with Multiple Pool for Blood Lead*



*** Derived from Marcus 1985a, 1985b, 1985c**

is associated with the erythrocytes in vivo (Boudene et al. 1977; Castellino and Aloj 1964; DeSilva 1981; Everson and Patterson 1980; Kehoe 1987; Lloyd et al. 1975; Morgan et al. 1977). Within 1 hour following the inhalation of tetramethyl lead, 61% and 39% of the inhaled dose was detected in the red blood cells and plasma, respectively (Heard et al. 1979). Over 50% of this erythrocyte lead pool is bound to hemoglobin, with lesser amounts bound to other proteins (Bruenger et al. 1973; Simons 1986). An in vitro study showed that fetal hemoglobin appears to have a greater affinity for lead than does adult hemoglobin (Ong and Lee 1980).

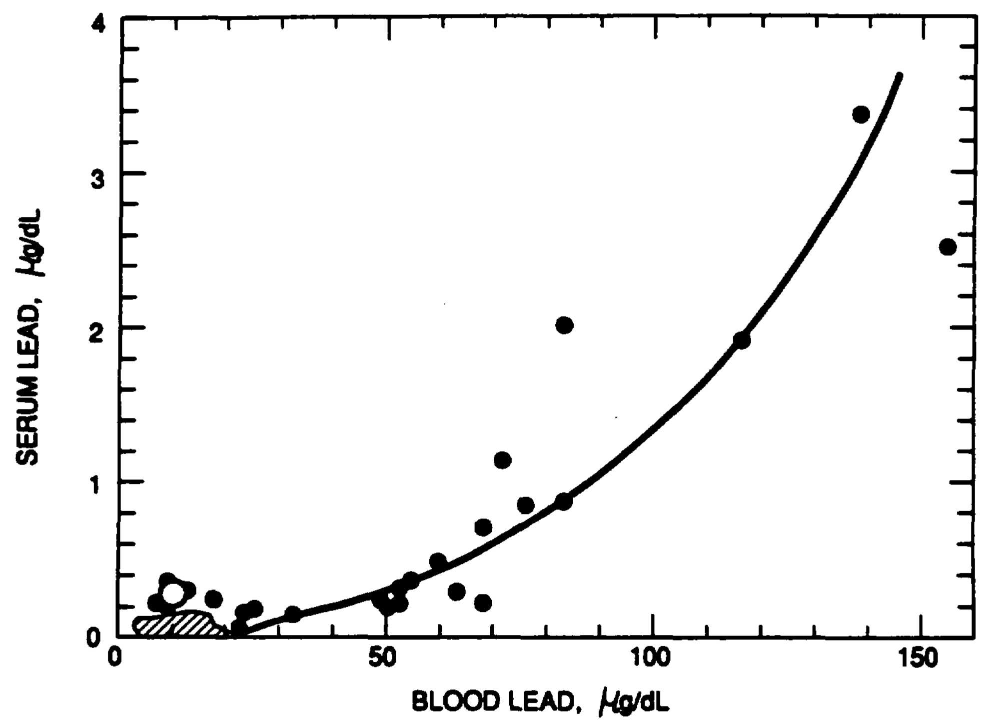
The relationship between the fractions of lead distributed in the erythrocytes and plasma has been described by Manton and Cook (1984) in patients with neurological disease and in control subjects including cases of plumbism. At blood lead levels ≤40 μg/dL, blood lead and serum lead levels increase linearly in a positive fashion; at higher blood lead levels, they assume a curvilinear relationship (Figure 2-5). The ratio of lead in plasma to that in whole blood increases dramatically at blood lead levels >40 μg/dL. In vitro data of the partitioning of blood lead between erythrocytes and plasma show a positive linear correlation at blood lead levels ≤100 μg/dL and deviation from linearity above that value (Clarkson and Kench 1958). The departure from linearity of this relationship in vivo at blood lead levels >40 μg/dL may be caused by altered cell morphology at high blood lead levels, resulting in a reduced availability or stability of lead binding sites in the erythrocytes (EPA 1986a; Gonick et al. 1985; Raghaven et al. 1980).

In human adults, approximately 94% of the total body burden of lead is found in the bones. In contrast, bone lead accounts for 73% of the body burden in children (Barry 1975). This large pool of lead in adults can serve to maintain blood lead levels long after exposure has ended (Kehoe 1987; O'Flaherty et al. 1982). Two physiological compartments appear to exist for lead in bones. In one compartment, bone lead is essentially inert, having a half-life of several decades. A labile compartment exists as well that allows for maintenance of an equilibrium of lead between bone and soft tissue or blood (Rabinowitz et al. 1976, 1977). The presence of labile lead may be a more accurate predictor of recent exposure or imminent toxicity than total body or whole blood burdens (EPA 1986a). In general, bone lead levels increase as a function of age. In 60–70-year-old men, the total bone lead content may be ≥200 mg, while children less than 16 years old have been shown to have total skeletal lead levels of 8 mg (Barry 1975). However, in some bones (i.e., mid femur and pelvic bone) the increase in lead content plateaus at middle age and then decreases at higher ages (Drasch et al. 1987). This decrease is most pronounced in females and may be due to osteoporosis.

Autopsies of occupational workers showed that the lead content in lungs and liver was elevated compared to control levels (Gerhardsson et al. 1986a). Autopsies of nonoccupational subjects revealed that males had higher lead content in tissues compared to females; however, sex differences in lead levels were not observed in tissues of children (Barry 1975). In most soft tissues (including brain), lead does not appear to accumulate as a function of age in humans over 20 years old (Barry 1975, 1981; Gross et al. 1975), but these data are based on limited sample size. Selective accumulation of lead has been observed in the hippocampus in both children and adults (EPA 1986a). However, this selective concentration of lead in hippocampus may be an artifact of the use of dry rather than wet weights in the analyses (Widzowski and Cory-Slechta 1991)

In animals, lead is widely distributed to soft tissues initially then redistributes and accumulates in bones. In general, the liver, lungs, and kidneys of rats showed the highest tissue lead concentrations immediately after acute exposure by inhalation (Boudene et al. 1977; Morgan and Holmes 1978), oral (Aungst et al. 1981), dermal (Kehoe and Thamann 1931; Laug and Kunze 1948), and intravenous routes (Castellino and Aloj 1964). The lead content in the bones gradually increased while levels in soft tissues began to decline

FIGURE 2-5. Curvilinear Relationship of Serum Lead to Blood Lead*



* Derived from Manton and Cook 1984

NOTE: Cross-hatched area represents several overlapping points.

and stabilize (Kehoe and Thamann 1931; Keller and Doherty 1980b). In a 12-month inhalation exposure to 0.0215 mg lead/m^3 (species of lead not specified) continuously in rats, lead content in kidney, liver, and lungs were increased at 6 and 12 months (Griffin et al. 1975b). The bone had the highest concentrations of lead. Lead concentration in the lung increased the least. Following the end of exposure, tissue levels declined except in the bone. A similar distribution pattern was observed in mice following intermediate exposure to lead nitrate (Kozlowski and Wojcik 1987).

The effects of aging on the tissue distribution of lead acetate was studied in male Fischer-344 rats in which the compound was administered in drinking water to juvenile (21-day-old), adult (8-month-old), and old (16-month-old) rats (Cory-Slechta 1990b; Cory-Slechta et al. 1989). Animals received 0, 1.27, and 6.37 mg lead/kg/day for 9.5 months (Cory-Slechta 1990b) or 0 and 4.5 mg lead/kg/day for 11 months (Cory-Slechta et al. 1989). Although the tissue lead distribution pattern (femur > kidneys > liver > brain) was similar for the three groups of animals, age-related increases in distribution were found in the brain and kidneys and a decline in lead content was found in the bones (femur). These age-related changes in tissue concentration may be the result of bone demineralization or prolonged tissue half-lives in older animals (Cory-Slechta 1990b). Retention was greater in suckling rats than adults following intraperitoneal exposure; brain levels were higher and kidney levels were lower in the pups (Kostial et al. 1978). One day after administration of the first dose of 50 mg lead/kg as lead acetate by gavage to neonatal rats, lead had accumulated in the liver, kidney, intestine, and intestinal contents (Miller et al. 1983). No lead was found in the blood, bone, or brain. Fifteen days after the first dose, and after the 50-mg/kg dose had been repeated for a total of five administrations, the highest concentration of lead was found in the femur. Brain lead levels had also increased. No accumulation of lead was observed in the lungs, heart, stomach, or spleen over the dosing period. Rat pups (4–8 weeks old) had a 2–3-fold increase in brain lead concentration when oral doses increased by 10-fold from 0.1 to 1 mg lead/kg (Collins et al. 1982). The highest brain lead level in these pups was in the hippocampus.

Transplacental transfer of lead in humans has been demonstrated in a number of studies, and lead has been identified in umbilical cord blood. In the work of Bellinger et al. (1987a), the mean lead concentration in umbilical cord blood from a sample size of greater than 11,000 women was 6.6±3.2 μg/dL. In a study of 236 pregnant women in Glasgow, Scotland, the geometric mean blood lead levels were 14 μg/dL for the mothers and 12 μg/dL in the umbilical cord at birth (Moore et al. 1982). Indirect evidence of transplacental transfer of lead in animals was suggested by the increased lead retention measured in the offspring of mice who received 157.3 mg lead/kg/day as lead acetate in drinking water during gestational days 11 or 14 (Donald et al. 1986b). Furthermore, lead can transfer through milk to suckling mouse litters if the mothers are exposed prior to or during lactation (Keller and Doherty 1980a).

Organic Lead. The highest lead levels were reported to be in liver, kidney, spleen, and lungs from autopsies (Gross et al. 1975). In a man and woman who accidentally inhaled a solvent containing 31% tetraethyl lead (17.6% lead weight to weight [w/w]) (Bolanowska et al. 1967), lead concentrations in the tissues, from highest to lowest, were liver, kidney, brain, pancreas, muscle, and heart. In another incident, a man ingested a chemical containing 59% tetraethyl lead (38% lead w/w) in which lead was highest in the liver followed by kidney, pancreas, brain, and heart (Bolanowska et al. 1967).

2.3.3 Metabolism

Inorganic Lead. Inorganic lead ion in the body is not known to be metabolized or biotransformed (Phase I processes); it does undergo Phase II processes. Primarily, it is absorbed, distributed, and then excreted, often in conjugated form (e.g., conjugated with glutathione) (EPA 1986a).

Organic Lead. Alkyl lead compounds are actively metabolized in the liver by oxidative dealkylation catalyzed by cytochrome P-450.

Relatively few human studies that address the metabolism of alkyl lead compounds were found in the available literature. The dealkylation, mediated by cytochrome P-450, of alkyl lead compounds is thought to occur in the rat, mouse, and rabbit. This step converts tetraethyl and tetramethyl lead to the triethyl and trimethyl metabolites, respectively, and inorganic lead (Bolanowska 1968; EPA 1986a; Kehoe and Thamann 1931). Further biotransformation of these intermediate metabolites is highly species-specific. Diethyl metabolite was not detected in rats receiving tetraethyl lead (Bolanowska 1968). Trialkyl lead metabolites were found in the liver, kidney, and brain following exposure to the tetraalkyl compounds in workers; these metabolites have also been detected in brain tissue of nonoccupational subjects (Bolanowska et al. 1967; Nielsen et al. 1978). In volunteers exposed by inhalation to 0.64 and 0.78 mg lead/m^3 of ^{203}Pb-labeled tetraethyl and tetramethyl lead, respectively, lead was cleared from the blood within 10 hours, followed by a reappearance of radioactivity back into the blood after approximately 20 hours (Heard et al. 1979). The high level of radioactivity initially in the plasma indicates the presence of tetraalkyl/trialkyl lead. The subsequent rise in blood radioactivity, however, probably represents water-soluble inorganic lead and trialkyl and dialkyl leads that were formed from the metabolic conversion of the volatile parent compounds (Heard et al. 1979).

2.3.4 Excretion

Inorganic Lead. Excretion of lead for all routes of exposure is discussed without subdividing data according to the route of exposure. In humans or animals, any dietary lead not absorbed by the gastrointestinal tract is eliminated in the feces (EPA 1986a). However the feces also includes an enterohepatic component. Airborne lead that has been swallowed and not absorbed is eliminated in a similar fashion. The lead that is not retained is either excreted by the kidney or excreted through biliary clearance into the gastrointestinal tract (EPA 1986a). For example, ingestion of 0.3–3.0 mg lead as lead acetate in drinking water per day for 16–208 weeks by adult volunteers resulted in excretion of greater than 85% of the ingested lead, of which over 90% was found in the feces (Kehoe 1987). Negligible amounts were eliminated in perspiration.

Urinary excretion of lead was observed at ≥1.0 mg lead per day after ingesting lead in the drinking water as lead acetate (Kehoe 1987). The urinary lead excretion in men after 3 months of continuous inhalation exposure to 0.011 mg lead/m^3 was approximately 85 μg lead/g urinary solids which was nearly double the pre-exposure baseline level of urinary excretion (Griffin et al. 1975b). Lead content in feces did not reveal any differences between the exposed and control groups (Griffin et al. 1975b). However, this may have been due to the relatively low concentration of lead used and the presence of lead in the diet. Moderately exposed workers were shown to have mean levels of lead in urine of 0.05–0.2 mg/L (Robinson 1974). The data suggest that 50–60% of the absorbed fraction of lead in adults in a steady-state condition with regard to lead intake/output was excreted on a short-term basis (Chamberlain et al. 1978; Rabinowitz et al. 1976). The half-life of this short-term fraction was found to be 19 days (Chamberlain et al. 1978). From comparison of data on lead kinetics for children and adults, infants apparently have a lower total excretion rate for lead (Rabinowitz et al. 1977; Ziegler et al. 1978). Infants from birth to 2 years of age have been shown to retain 31.7% of the total amount of lead absorbed (Ziegler et al. 1978), whereas adults retained only 1% retention of an absorbed dose of lead (Rabinowitz et al. 1977).

In general, there is a greater excretion of lead in feces than in urine of animals following acute, intermediate, and chronic exposure. Species differences exist in the rate and extent of total lead excretion. Rats excreted 55% after 5 days (Morgan et al. 1977) and 66% after 8 days (Momcilovic and Kostial 1974). Six days after inhalation of 0.01 mg/m^3 lead for 30–45 minutes in Wistar rats, 40% and 15% of the dose was eliminated in the feces and urine, respectively (Boudene et al. 1977). After rats received an intravenous dose of lead, 45.3% of the administered dose was excreted 6 days postexposure (Castellino and Aloj 1964). Total excretion of lead was 7.29% and 18.3% of a single oral exposure to 6.37 mg/kg as lead acetate in young and adult rhesus monkeys, respectively (Pounds et al. 1978). Three weeks following intravenous administration of lead, beagles excreted approximately 50% of the dose of which 75% was detected in the feces (Lloyd et al. 1975). Adult mice excreted 62% of injected lead by 50 days; cumulative lead in feces was 25–50% (Keller and Doherty 1980a; Kostial and Momcilovic 1974). Fecal excretion was relatively constant (6% of the dose per day) during the 30-day recovery period in mice fed wheat grain containing 3.38, 83.2, or 171.1 mg lead/kg as lead nitrate for up to 40 days (Kozlowski and Wojcik 1987). However, urinary excretion was not measured. With chronic lead exposure, the average fecal and urinary lead concentrations in rats and rhesus monkeys exposed to 0.0215 mg lead/m^3, 22 hours per day, for a year, were higher than controls, with lead content greater in the feces than in the urine; however, there were high individual variations in the excretion rate (Griffin et al. 1975b).

Lead can also be excreted in the bile (Klaassen and Shoeman 1974). In the rat, initial excretion occurs in the urine, followed by greater excretion in the feces following intravenous administration (Castellino and Aloj 1964; Klaassen and Shoeman 1974; Morgan et al. 1977). As the dose increases, the proportion of the lead excreted into the gut via bile increases then plateaus at 3 and 10 mg/kg (Klaassen and Shoeman 1974). Biliary excretion of lead is suggested to be a saturable process (Gregus and Klaassen 1986). Excretion of lead in the bile by dogs amounted to approximately 2% of that by rats, and biliary excretion of lead by rabbits amounted to approximately 40% of that by rats (Klaassen and Shoeman 1974).

In rats, excretion of lead was biphasic following intravenous administration, with half-lives of 21 hours for the fast phase and 280 hours for the slow phase (Morgan et al. 1977). Dogs excreted lead in three phases, with half-lives of 12, 184, and 4,951 days (Lloyd et al. 1975). The half-life of the terminal phase of a biphasic elimination curve for mice was 110 days (Keller and Doherty 1980a).

Organic Lead. Urinary lead levels were elevated for the 4 days in a man accidentally exposed to an unknown quantity of tetramethyl lead (Gething 1975). Exhalation of the tetraalkyl lead compounds following inhalation exposure is a major route of elimination in humans. At 48 hours postexposure, 40% and 20% of the initially inhaled tetramethyl and tetraethyl lead doses, respectively, were exhaled with low urinary excretion (Heard et al. 1979).

2.4 RELEVANCE TO PUBLIC HEALTH

Humans living in areas surrounding hazardous waste sites may be exposed to lead via ingestion of contaminated water or soils or by inhalation of lead particles in the air. For the general population (i.e., those not living in the vicinity of hazardous waste sites), the major route of exposure to lead is ingestion of lead-contaminated drinking water, food, soil, lead-based paint chips, or dusts (these two latter routes are particularly relevant to children in lower-income urbanized populations). For occupationally exposed individuals, the predominant route of exposure is the inhalation of lead particles.

Lead has been shown to affect virtually every organ and/or system in the body in both humans and animals. The most sensitive target organs of lead appear to be the nervous system (particularly in children), the hematopoietic system, and the cardiovascular system. There is evidence in both humans and animals to suggest that the kidney and the immune system are also adversely affected by lead. Lead has also been shown to be carcinogenic in animals. The adverse health effects noted in humans are generally supported by observations in laboratory animals. No MRLs have been developed for lead because a threshold has not yet been defined for the most sensitive effects of lead (i.e., neurotoxicity).

The lack of a clear threshold for health effects and the need to consider multi-media routes of exposure makes evaluating the risks from exposure to lead in the environment very difficult. In addition, factors such as absorption potential of the lead compound of interest, and age and nutritional status of the population prevents the development of generic guidance. Despite these complexities, guidance is needed for the assessment of risk to humans from exposure to lead at NPL sites. Such guidance must be adaptable to site-specific information regarding exposure sources and demographic data as well as provide default values where data may not be available in order to generate quantitative estimates of risk (DeRosa et al 1991).

Numerous studies have attempted to correlate environmental lead levels with blood lead levels (Table 2-5). Slope factors have been calculated which attempt to predict increases in blood lead (μg/dL) per unit lead concentration in environmental media (EPA 1986a, 1989g). The relationship between media concentration and blood lead is curvilinear such that the slopes decrease with increasing lead concentrations.

Air slope factors calculated from experimental and cross-sectional studies range from a 1–2.7 μg/dL increase in blood lead per μg/m^3 air lead concentration. A slope factor of 1.92±0.60 for children was calculated by Angle et al. (1984) from a study conducted between 1971 and 1977 in three areas of Omaha, Nebraska (Angle and McIntyre 1979). This study provides some of the most useful and relevant information in that covariates (eg. age, dust exposure, sex) were controlled. EPA analysis of two other reliable studies provide comparable slope factors for children of 2.46±0.58 (Roels et al. 1980) and 1.53±0.064 (Yankel et al. 1977).

Studies correlating water concentration and blood lead are difficult to compare due to the wide range of water lead concentrations in the studies--50–2,000 μg/L (EPA 1986a). Over a wide range of water lead concentrations, the relationship to blood levels is curvilinear; however, at typical ambient water levels in the United States, the relationship appears to be linear. Pocock et al. (1984) provide the most reliable data for adults at the lower range of water lead concentrations (<100 μg/L). Their slope factor estimates a blood lead of 0.06 μg/dL per μg lead/L water. Lacey et al (1985) provide data for infants. Regression analysis of their data gives two slope factors, 0.26 μg/dL blood per μg/L water at water lead levels below 15 μg/L and 0.04 μg/dL blood per μg/L water at water lead levels above 15 μg/L (EPA 1991a).

The most reliable slope factors for the blood lead contribution from diet in adults can be obtained from an experimental study (Cools et al. 1976) and a duplicate diet study (Sherlock et al. 1982). These slope factors range from 0.027–0.034 μg/dL blood per μg lead intake/day (EPA 1986a). The data from the duplicate diet infant study by Ryu et al (1983) were reanalyzed to derive a slope factor of 0.24 μg/dL blood per μg/day lead intake (EPA 1990e).

Studies relating soil lead levels to blood lead levels are difficult to compare. The relationship depends on depth of soil lead sampled, sampling method, cleanliness of the home, age of the children, and mouthing activities, among other factors. Slopes range between 0.0007 and 0.0068 μg/dL blood lead increase per mg/kg soil lead. Angle et al (1984) provide the most conservative slope estimates based on the Omaha childhood blood data. They compared their power function model against a linear model for the Omaha study and concluded that the linear model which predicted a slope of 0.0068, was "statistically equivalent" to the power model and provided more biologically credible blood lead curves. They also determined similar slopes for dust, 0.0072 μg/dL blood lead increase per mg/kg house dust lead (Angle et al. 1984).

As previously stated, in order to provide health-based guidance an approach must be used that utilizes site- and media-specific information. ATSDR is currently developing guidance that employs this approach. For a given site, slope factors can be used with environmental data to predict media-specific contributions to blood lead. Summation of the individual media contributions will yield a total predicted blood lead level. The uncertainties in predicting mean blood leads can be estimated by using the standard errors associated with the slope values to generate a range of predicted blood leads. Proposed default values can be used in lieu of missing environmental data.

By predicting blood lead levels, a determination can be made about what health impacts may be occurring at a given site. This will assist health assessment personnel in deciding whether further action is needed. However, any guidance should be used strictly as guidance and not utilized for recommending "safe levels" or remediation goals. A site-specific evaluation must be made before reaching any conclusions (e.g., pica children, ground cover over contaminated soil, nutritional status and age of the population, etc.).

Death. Death can be the end result in cases of severe lead encephalopathy in both adults and children. The National Academy of Sciences (NAS 1972) analyzed unpublished data obtained from the patient populations reported in Chisolm (1962, 1965) and Chisolm and Harrison (1956) and concluded that the range of blood lead levels associated with death from lead encephalopathy in children was approximately 125–750 μg/dL (mean = 327 μg/dL).

The results of mortality studies conducted on occupationally exposed workers are discrepant, and all the studies have design flaws that render them limited with regard to the validity of the conclusions that can be drawn from their results. One study found a statistically significant increase in mortality due to malignant neoplasms, chronic renal disease, and "ill-defined" causes in lead-exposed workers (Cooper 1988; Cooper et al. 1985). Another study found a statistically significant increase in mortality due to cardiovascular disease in lead-exposed workers (Fanning 1988), and another found a statistically significant increase in the incidence of deaths from cerebrovascular disease in lead-exposed newspaper printers (Michaels et al. 1991). A fourth study found no statistically significant increase in mortality due to lead exposure (Gerhardsson et al. 1986b). Slightly lower blood lead levels were recorded in the study by Gerhardsson et al. (1986b) than in the study by Cooper et al (1985). It is unclear what impact these slightly lower levels may have had on the study outcome.

High levels of lead have been suggested as a causative agent in SIDS. Investigators have found that babies who died of SIDS had a greater number of the highest lead levels in dry blood (blood samples in which the water has been removed) as compared to control (alive or dead due to traumatic causes) babies (Drasch et al. 1988). These results suggest that there may be an association between high lead body burden and SIDS, but the mechanism behind this association cannot be determined at this time. Possibilities include an effect of lead on prenatal and/or postnatal neurological development.

TABLE 2-5. Summary of Blood Slope Factors from Various Environmental Media

Population	Slope	Comments	References
Air Slope Factors:	µg/dL per µg Pb/m^3		
Adults; N = 43	1.75±0.35	Experimental study; EPA analysis	Griffin et al. 1975
Adults: N=5	1.59–3.56	Experimental study; EPA analysis Calculated	Rabinowitz et al. 1974, 1976, 1977
Adults; N=10	2.7	Experimental study; EPA analysis	Chamberlain et al. 1978
Children; 1–18 years of age; N=831; 1074 blood samples	1.92±0.60	Omaha cross-sectional study; smelter	Angle et al. 1984
Children; N=148	2.46±0.58	Belgium cross-sectional study; smelter; EPA analysis	Roels et al. 1980
Children; N=880	1.53±0.064	Kellogg/Silver Valley cross-sectional study; EPA analysis; smelter	Yankel et al. 1977
Adult males; 5 groups, 30/group	2.57±0.04	Cross-sectional study; at air concentration of 1 µg/m^3	Azar et al. 1975
Adult males; 5 groups, 30/group	1.12	Reanalysis of Azar 1975 by Snee 1982; at air concentration of 1 µg/m^3	Azar et al. 1975
Adult males; 5 groups, 30/group	1–2.39	Analysis of Azar 1975 by EPA; at 1 µg/m^3	Azar et al. 1975
Water Slope Factors:	µg/dL per µg Pb/L		
Infants N=131	0.25 at <15 µg Pb/L; 0.04 at >15 µg Pb/L	Scottish study of infants; EPA analysis	Lacey et al. 1985
School children N=495	0.16 at <15 µg Pb/L; 0.03 at >15 µg Pb/L	Scottish study; EPA analysis	Laxen et al. 1987
Adult males N=7,735	0.06	24 British towns sampled; water lead levels <100 µg/L	Pocock et al. 1983
Adult Females N=114	0.03	Duplicate diet study; Ayr, Scotland; EPA analysis	Sherlock et al. 1982

TABLE 2-5 (Continued)

Population	Slope	Comments	References
Diet Slope Factors:	μg/dL per μg Pb Ingested/Day		
Infants and toddlers; N=29	0.24	Breast-fed and formula-fed; EPA analysis	Ryu et al. 1983 EPA 1990e
Adults; N=31	0.034--females	Duplicate diet study; Ayr, Scotland	Sherlock et al. 1982
Adults; N=15	0.014–0.017--males; 0.018–0.022--females	Experimental study; blood leads were not allowed to equilibrate	Stuik et al. 1974
Adult males; N=15	0.027	Experimental study	Cools et al. 1976
Soil Slope Factors:	μg/dL per mg Pb/kg		
Mixed	0.002–0.016	Review of the literature	Reagan and Silbergeld 1989
Children; 1-18 years of age; N=831; 1,074 blood samples	0.0068±0.00097	Omaha study; urban/suburban	Angle et al. 1984
Children; 1–72 months of age; N=377; 926 blood leads	-0.00016–0.00223 (soil near house) 0.00073–0.0023 (soil at curb)	New Haven, CT; EPA analysis. The largest slopes were from the children under 1 year of age with SE=0.00091 (at house) and 0.0019 (at curb)	Stark et al. 1982
Children; N=880	0.0011 (avg. for all ages) 0.0025 (for 2–3 year olds)	Kellogg/Silver Valley cross-sectional study; smelter; EPA analysis	Yankel et al. 1977

TABLE 2-5 (Continued)

Population	Slope	Comments	References
Dust Slope Factors:	μg/dL per mg Pb/kg		
Children; 1–18 years of age; N=831; 1074 blood samples	0.00718±0.00090	Omaha study; urban/suburban; housedust	Angle et al. 1984
Children; 1–6 years of age; N=32	0.008	Homes of lead workers; housedust	Baker 1977
Children; 2 years of age; N=82	0.004	Area of high lead soil; housedust	Baltrop et al. 1974
Adults and children; N=80	0.0086–0.0096 (housedust); 0.0021–0.0067 (outside dust)	Smelter	Roberts et al. 1974
Children; N=377; 1-72 months of age; 926 blood lead levels	0.00402±0.0017 (0–1 year old); 0.00182±0.00066 (2–3 year old) 0.00022±0.00077 (4–7 year old)	New Haven, CT; EPA analysis	Stark et al. 1982

Adapted from Duggan and Inskip 1985; EPA 1986a, 1989g

Oral LD_{LO} values in a number of species are available for lead (see Table 2-3). Mortality data from longer-term studies in animals are often inconclusive. However, based on the information available in humans, it is apparent that high body burdens of lead can result in death, which is most often secondary to lead-induced encephalopathy.

Systemic Effects

Respiratory Effects. There are no conclusive data available to indicate that lead adversely affects the respiratory system in humans. However, one inhalation study in animals indicates that continuous prolonged (28-day) exposure to lead nitrate particles may be irritating to the lungs, as evidenced by the pulmonary edema and hemorrhage seen in the lungs of the lead-exposed mice at necropsy (Hillam and Ozkan 1986). These effects were not seen in animals continuously exposed for 14 days, suggesting that the apparent adverse respiratory effects were dependent on the duration of exposure and are cumulative. However, the irritative properties of inhaled lead depend partially on the solubility and pH of the species. In this study, the animals were exposed to lead nitrate, which is acidic and therefore, irritating. Therefore, based on these results, it cannot be determined whether prolonged inhalation exposure of humans to high levels of lead particles other than lead nitrate, such as may occur in populations living in the vicinity of hazardous waste sites where dust particles may contain a high concentration of lead, may result in pulmonary irritation.

Cardiovascular Effects. The evidence from occupational, clinical, and general population studies suggests that lead affects the cardiovascular system in humans, producing cardiac lesions and electrocardiographic abnormalities at high levels of exposure and increases in blood pressure, particularly in middle-aged men, at very low levels of exposure with no evident threshold through the lowest blood lead levels, 7 μg/dL. The contribution of lead, compared with many other factors that affect blood pressure, appears to be relatively small, usually not accounting for more than 1-2% of the variation explained by the models employed when other significant factors are controlled for in the analyses (EPA 1986a). In summary, the evidence in humans does not, at this time, permit any conclusions to be drawn regarding a positive association between increased blood lead levels and blood pressure.

The animal data clearly demonstrate that lead increases blood pressure, despite confounding experimental design factors such as species tested, age of animals, route of administration, dose used (doses that are high enough to induce nephrotoxicity may produce hypertension as a secondary effect), method of measuring blood pressure, and use of anesthesia.

Interpretation of the blood lead-blood pressure data in epidemiological studies of the general population remains an area of controversy, as reflected in the 1987 Symposium on Lead-Blood Pressure Relationships (Environmental Health Perspectives, Volume 78, June 1988) sponsored by the University of North Carolina at Chapel Hill, the International Lead Zinc Research Organization, Inc., EPA, and the American Heart Association, the negative population studies (Elwood et al. 1988; Grandjean et al. 1989; Neri et al. 1988; Pocock et al. 1988; Staesson et al. 1990, 1991), and the reanalyses of the NHANES II data by Coate and Fowles (1989) and Gartside (1988). As summarized by Victery et al. (1988), both S.J. Pocock and J. Schwartz, in considering the evidence from general population epidemiological studies, concluded that a doubling of blood lead levels appeared to be associated with an increase of approximately 1-2 mmHg in systolic blood pressure. Pocock concluded that the overall evidence from the human studies did not permit the inference of a causal relationship between blood lead and blood pressure. Schwartz concluded that, although a causal inference could not readily be drawn from the epidemiological data alone, such an inference was consistent with the animal data. Based on the data for both humans and animals, Schwartz concluded that a causal relationship is likely.

Several mechanisms for lead's purported effects on blood pressure have been proposed, based on experimental findings. These include effects on several hormonal and neural regulatory systems, changes in vascular smooth muscle reactivity, cardiac muscle contractility, changes in cell membrane cation transport systems, and possible effects on vascular endothelial cells (Victery 1988). On a cellular level, it has been noted that lead causes increased intracellular concentrations of calcium in brain capillaries, neurons, osteoclasts, hepatocytes, and arteries. Increased intracellular calcium is the trigger for smooth muscle contraction; therefore, increased intracellular calcium stores may result in increased vascular smooth muscle tone. Furthermore, lead has been found to interfere with cellular calcium metabolism; it activates calmodulin in its role of activating phosphodiesterase, the enzyme that converts cAMP into AMP. cAMP is involved in stimulating the calcium pump that removes calcium from the cytosol into the endoplasmic reticulum. This would be expected to reduce reactivity and tone, and a lead effect on increasing the conversion of cAMP into AMP would be expected to increase reactivity and tone (Schwartz 1988). Alternatively, it has been suggested that lead-induced hypertension may be partially mediated by altered activity of the protein kinase C branch of the calcium messenger system, which would, in turn, result in increased vascular reactivity (Chai and Webb 1988).

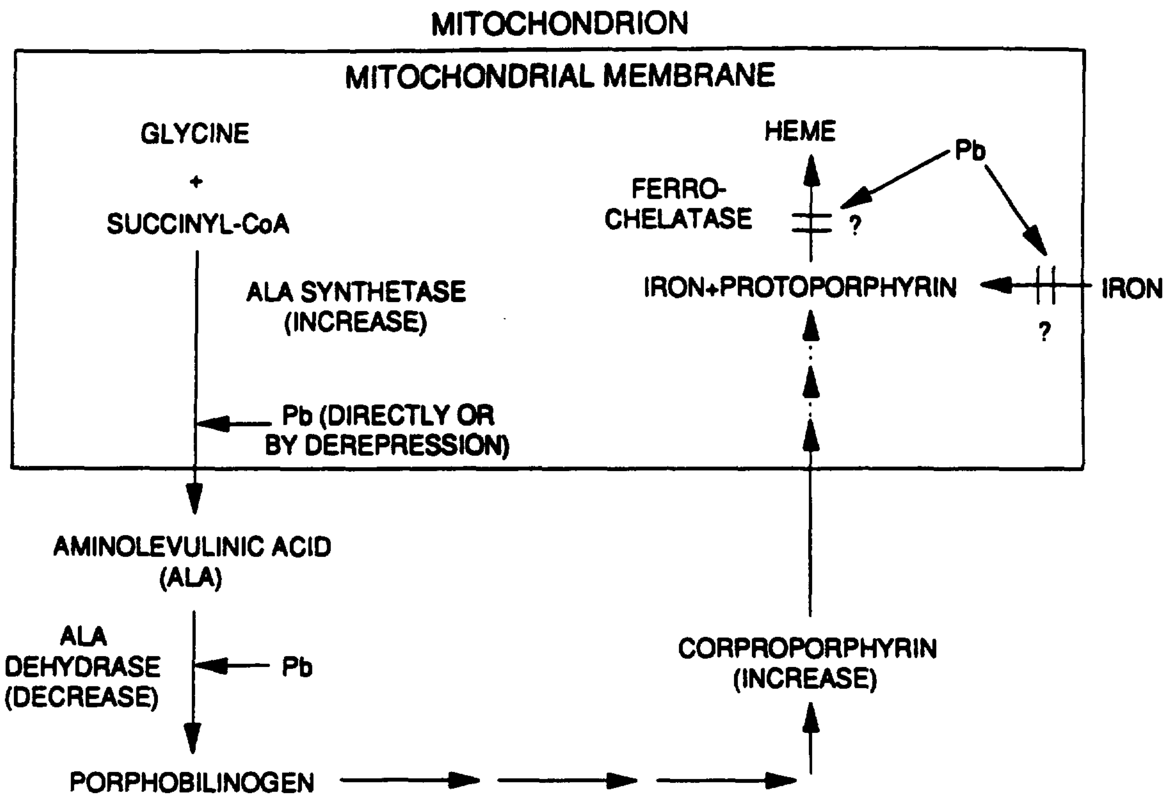
Limited data on occupationally exposed men indicate that the effect of lead on blood pressure may be mediated in part through the renin-angiotensin system, as evidenced by lead-related increases in plasma renin and angiotensin I levels (Campbell et al. 1985) and the kallikrein-kinin system, as indicated by a correlation between renin and kallikrein (Boscolo et al. 1981). Evidence from patients with essential hypertension and renal impairment suggests that excessive lead absorption may be involved in the development of both conditions (Batuman et al. 1983).

In reviewing the voluminous database on the mechanism of lead's hypertensive action in animals, EPA (1986a) concluded that although lead, even at very low levels, produces effects on the renin-angiotensin system in animals, these changes are not established as the cause of hypertension. Rather, hypertension is more likely to be due to changes in vascular reactivity and level of sympathetic tone, both of which may be dependent on lead-related changes in intracellular calcium ion concentration (EPA 1986a).

Gastrointestinal Effects. Colic, which is characterized by a combination of abdominal pain, constipation, cramps, nausea, vomiting, anorexia, and weight loss, is a consistent early symptom of lead poisoning in occupationally exposed cases or in individuals acutely exposed to high levels of lead. Colic is also seen in children with lead poisoning. Histopathological evidence of lead-induced gastrointestinal damage has not been reported. Adverse gastrointestinal effects have not been noted in animal studies, but it is difficult to study the symptoms of colic that are noted in humans in the laboratory situation.

Hematological Effects. Lead effects on the hematopoietic system have been well documented. These effects, which are seen in both humans and animals, include increased urinary porphyrins, coproporphyrins, and ALA, EP, FEP, ZPP, and anemia. The process of heme biosynthesis is outlined in Figure 2-6. Lead interferes with heme biosynthesis by altering the activity of three enzymes: ALAS, ALAD, and ferrochelatase. Lead indirectly stimulates the mitochondrial enzyme ALAS, which catalyzes the condensation of glycine and succinyl-coenzyme A to form ALA. The activity of ALAS is the rate-limiting step in heme biosynthesis; increase of ALAS activity occurs through feedback derepression. Lead competitively inhibits the zinc-containing cytosolic enzyme ALAD, which catalyzes the condensation of two units of ALA to form porphobilinogen. Inhibition of ALAD and feedback derepression of ALAS result

FIGURE 2-6. Effects of Lead on Heme Biosynthesis*



* Derived from EPA 1986a

in accumulation of ALA. Lead decreases the activity of the mitochondrial enzyme ferrochelatase, which catalyzes the insertion of iron (II) into the protoporphyrin ring to form heme. The action of lead on this enzyme occurs either by direct inhibition through competition with the zinc chelating center or by alteration of intramitochondrial transport of iron (EPA 1986a).

Lead inhibition of ferrochelatase results in an accumulation of protoporphyrin IX, which is present in the circulating erythrocytes as ZPP, because of the placement of zinc, rather than iron, in the porphyrin moiety. ZPP is bound in the heme pockets of hemoglobin and remains there throughout the life of the erythrocyte. Assays used in studies of protoporphyrin accumulation measure ZPP or FEP, because ZPP is converted to FEP during extraction. Because accumulation of ZPP occurs only in erythrocytes formed during the presence of lead in erythropoietic tissue, this effect is detectable in circulating erythrocytes only after a lag time reflecting maturation of erythrocytes and does not reach steady state until the entire population of erythrocytes has turned over, in approximately 120 days (EPA 1986a).

A marked interference with heme synthesis results in a reduction of the hemoglobin concentration in blood. Decreased hemoglobin production, coupled with an increase in erythrocyte destruction, results in a hypochromic, normocytic anemia with associated reticulocytosis. Decreased hemoglobin and anemia have been observed in lead workers and in children with prolonged exposure at higher blood lead levels than those noted as threshold levels for inhibition or stimulation of enzyme activities involved in heme synthesis (EPA 1986a).

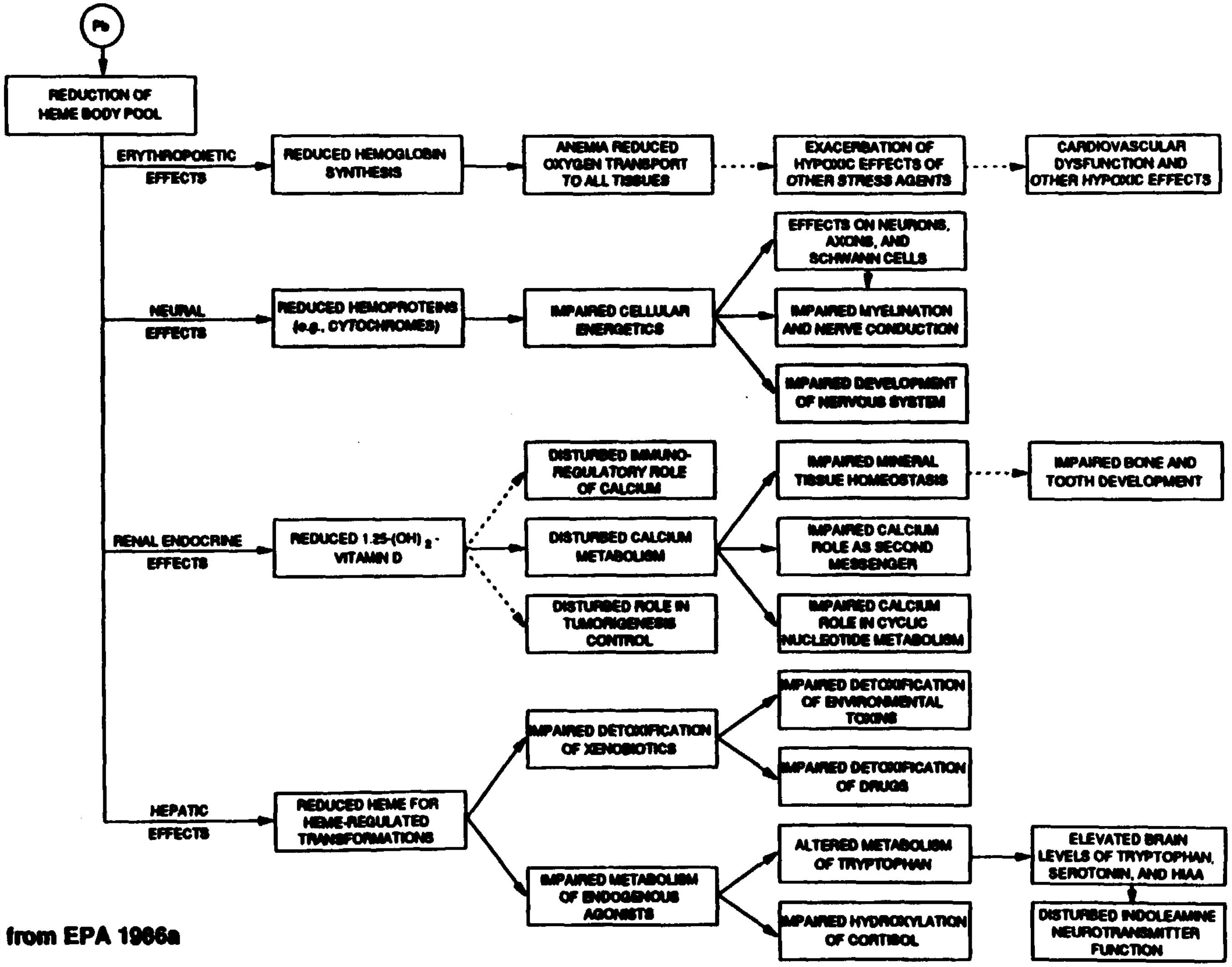
The increase in erythrocyte destruction may be due in part to inhibition by lead of pyrimidine-5'-nucleotidase, which results in an accumulation of pyrimidine nucleotides (cytidine and uridine phosphates) in the erythrocyte or reticulocyte. This enzyme inhibition and nucleotide accumulation affect erythrocyte membrane stability and survival by alteration of cellular energetics (Angle et al. 1982; EPA 1986a).

Formation of the heme-containing cytochromes is inhibited in animals treated intraperitoneally or orally with lead compounds. An inverse dose-effect relationship between lead exposure and P-450 content of hepatic microsomes and also activity of microsomal mixed-function oxygenases has been observed (Goldberg et al. 1978). Increasing duration of exposure to lead was associated with decreasing microsomal P-450 content and decreasing microsomal heme content (Meredith and Moore 1979). In addition, delays in the synthesis of the respiratory chain hemoprotein cytochrome C have been noted during administration of lead to neonatal rats (Bull et al. 1979).

The impairment of heme synthesis by lead has a far-ranging impact not limited to the hematopoietic system. EPA (1986a) summarized the known and potential consequences of the reduction of heme synthesis as shown in Figure 2-7. One of these consequences, the decrease in cytochrome P-450 content and related enzyme activities in many tissues, is summarized above.

Effects on some steps in the heme synthesis pathway occur at very low exposure levels, but there is some controversy as to the toxicological significance of a depression in ALAD activity in the absence of a detectable effect on hemoglobin levels. EPA (1986a) and ATSDR (1988) are concerned about effects on the heme synthesis pathway, however, because of the emerging evidence of a constellation of effects, including inhibition of ALAD and pyrimidine-5'-nucleotidase activities, elevations in EP levels, reductions in serum 1,25-dihydroxyvitamin D levels, and also subtle neurobehavioral, electrophysiological, growth and blood pressure effects at low blood lead levels (10–15 μg/dL and possibly lower).

FIGURE 2-7. Multiorgan Impact of Reduction of Heme Body Pool by Lead*



* Derived from EPA 1986a

Musculoskeletal Effects. Individuals who have had high exposures to lead, either occupationally or by the consumption of alcohol from lead stills have been reported to exhibit a bluish-tinged line in the gums (i.e., the "lead line"). In addition, case reports of high occupational exposure to lead have described the occurrence of muscle weakness, cramps, and joint pain. The mechanism by which lead may induce these musculoskeletal effects is not known, but may involve competition between lead, calcium, and zinc.

Hepatic Effects. Limited evidence exists to suggest that lead affects hepatic mixed function oxygenases by inhibiting the formation of the heme-containing protein, cytochrome P-450 (Alvares et al. 1975; Saenger et al. 1984). Abnormal liver function in individuals exposed to high levels of lead could not be conclusively linked to lead because prior medical histories were not known. Studies in animals provide limited evidence that lead may affect the liver. Effects reported in the literature include effects on hepatic glycogen and DNA content and the ability to incorporate amino acids into proteins (Barratt et al. 1989; Giurgea et al. 1989). This evidence is not conclusive because these end points are relatively non-specific, and no histopathological evaluation or organ function tests (i.e., serum enzymes) were performed. Based on the information available in humans and animals, it is difficult to conclude that lead adversely affects the liver.

Renal Effects. Exposure to lead that results in blood levels ranging from approximately 40 to >100 μg/dL has been associated with nephropathy in lead-exposed workers. The characteristics of early or acute lead-induced nephropathy in humans include nuclear inclusion bodies, mitochondrial changes, and cytomegaly of the proximal tubular epithelial cells; dysfunction of the proximal tubules (Fanconi's syndrome) manifested as aminoaciduria, glucosuria, and phosphaturia with hypophosphatemia; and increased sodium and decreased uric acid excretion. These effects appear to be reversible. Characteristics of chronic lead nephropathy include progressive interstitial fibrosis, dilation of tubules and atrophy or hyperplasia of the tubular epithelial cells, and few or no nuclear inclusion bodies, reduction in glomerular filtration rate, and azotemia. These effects are irreversible. The acute form is reported in lead-intoxicated children, whose primary exposure is via the oral route, and sometimes in lead workers. The chronic form is reported mainly in lead workers, whose primary exposure is via inhalation. Animal studies provide evidence of nephropathy similar to that in humans, and particularly to the acute form.

In human studies where no renal biopsies have been performed to prove conclusively the occurrence of nephropathy, the results have not been consistent. This could partially be explained by the choice of the renal function parameter studied. The only parameter of renal function shown to be affected in some studies is an increase in the levels of NAG. NAG is a lysosomal enzyme present in renal tubular cells that has been shown to be a sensitive indicator of early subclinical renal tubular disease. Increases in NAG in lead-exposed individuals have been seen at relatively low blood levels (i.e., ≤62 μg/dL), which suggests that lead may affect renal tubular function to a greater extent than glomerular function. The mechanism by which lead affects the release of NAG from renal tubular cells is not known, but it is suggested that lead could attach to kidney cell membranes and alter membrane permeability.

Excessive lead exposure has also been implicated as a causative agent in kidney disease associated with gout and essential hypertension (Batuman et al. 1981, 1983). It was found that gout patients with renal impairment and hypertensive patients with renal impairment had significantly higher lead stores (as determined by the 3-day EDTA lead mobilization test) than gout patients or hypertensive patients without renal impairment, respectively. Therefore, excessive lead absorption may somehow be involved in the renal impairment seen in patients with gout or essential hypertension.

Children appear to have a higher threshold for lead-induced nephropathy than adults. According to the National Academy of Sciences (NAS 1972), Fanconi's syndrome is estimated to occur in approximately 1/3 of children with encephalopathy and blood lead levels of approximately 150 μg/dL. Based on several studies conducted in children known to have lead toxicity, it appears that nephropathy occurs in children only at blood levels >80 μg/dL, and usually exceeding 120 μg/dL (NAS 1972).

As discussed above, the hypertensive effects of lead may be mediated through effects on the kidney. Lead appears to affect vitamin D metabolism in renal tubule cells, such that circulating levels of the vitamin D hormone, 1,25-dihydroxyvitamin D, are reduced. This effect is discussed later in this section: Other Systemic Effects.

Dermal/Ocular Effects. Visual problems have been noted in human studies. These are mostly anecdotal in nature and not well documented.

Long-term scotopic visual system deficits have been observed in laboratory animals following low-level exposure during early postnatal development. A series of experiments conducted in rats to determine whether these effects are secondary to an effect on the central nervous system or are the result of a direct effect on the eye following low-level exposure during early postnatal development demonstrated that lead has adverse effects on the rods of the retina. This was evidenced by changes in single-flash electroretinograms, selective degeneration of rod (but not cone) photoreceptor cells, accumulation of glycogen particles in the retinas, decreased retinal sensitivity and rhodopsin content, and a decrease in rod outer segment length with a selective loss of 20% of the rod cells (Fox and Chu 1988; Fox and Farber 1988; Fox and Rubinstein 1989). These investigators also demonstrated that most of the effects occur within the first 30 days of life, although the changes remain throughout the 1st year. A possible mechanism of action for this selective adverse effect on the rods of the retina was proposed. This effect could be due to a lead-induced alteration in cyclic nucleotide metabolism resulting in a change in the activity of the sodium channels in the rods. To investigate this possibility, cyclic nucleotide content and the activity of the enzymes associated with their metabolism were measured. A significant increase in cGMP but not cAMP was found in the lead-treated rats. This increase in cGMP content was in turn found to be associated with decrease cGMP-PDE activity (Fox and Farber 1988).

Other Systemic Effects. Evidence from occupationally exposed workers suggests that lead may adversely affect thyroid function. A weak but statistically significant negative correlation was found between duration of exposure to lead and thyroxin and free thyroxin levels in workers with blood lead levels that were ≥56 μg/dL (Tuppurainen et al. 1988). Three possible mechanisms were proposed to account for this effect: a direct effect of lead on the thyroid gland; an effect on the hypothalamopituitary level; and an effect on the peripheral turnover of thyroid hormones.

Adverse effects on the thyroid have not been observed in children, however. In a study of inner-city children, linear regression analysis revealed that there was no association between blood lead levels and either thyroxin or free thyroxin (Siegel et al. 1989). Four possible explanations were posed by the authors to account for this apparent lack of effect of lead on thyroid function in children. First, children may be less susceptible than adults to the toxic effects of lead on the thyroid gland. However, this is not consistent with the greater susceptibility of children to the other toxic effects of lead (e.g., neurotoxicity). Second, the lead-exposed workers had higher blood lead levels than the children in this study (51.9 μg/dL versus 25 μg/dL). However, no effect on thyroxin was seen even in children with blood levels ≥60 μg/dL. Third, the workers had a longer duration of exposure (average exposure of 5.8 years versus 2.8 years in the children). Finally, thyroxin levels may not be a sensitive enough indicator of thyroid function. In addition, the iodine content of the adult versus children's diet should be compared because iodine intake affects thyroid function. Nevertheless, the available data suggest that adults with potential for high levels of lead exposure may be at risk for thyroid toxicity.

Lead appears to interfere with the conversion of vitamin D to its hormonal form, 1,25-dihydroxyvitamin D. In lead-exposed children with blood lead levels of 33–55 μg/dL, 1,25-dihydroxyvitamin D levels were reduced to levels comparable to those observed in children with severe renal insufficiency (Rosen et al. 1980). In lead-exposed children with blood lead levels of 33–120 μg/dL, 1,25-dihydroxyvitamin D levels were depressed to levels (≤20 pg/mL) comparable to those found in vitamin D-dependent rickets, type I--an inborn error of vitamin D metabolism in which the 1-hydroxylase system or component thereof is virtually absent (Rosen and Chesney 1983; Rosen et al. 1980). These comparisons are consistent with an effect of lead on the production of 1,25-dihydroxyvitamin D by renal 1-hydroxylase. However, in children with low to moderate lead exposure (average lifetime blood lead levels ranging from 4.8–23.6 μg/dL) and adequate dietary intake of calcium, phosphorus, and vitamin D, no effect was observed on vitamin D metabolism, calcium and phosphorus homeostasis, and bone mineral content (Koo et al. 1991). Based on these results, it appears that adverse effects on vitamin D metabolism may be manifested only at chronically high lead exposures in children deficient in calcium, phosphorus, and vitamin D.

It is possible that lead's interference with heme synthesis may underlie the effects on vitamin D metabolism. Evidence that lead affects heme synthesis in the kidney was presented in the section on hematological effects. In addition, apparent thresholds for the effects of lead on renal vitamin D metabolism and for erythrocyte protoporphyrin accumulation are similar.

Because the vitamin D-endocrine system is responsible in large part for the maintenance of extra- and intracellular calcium homeostasis, it is reasonable to conclude that the interference of lead with renal 1,25-dihydroxyvitamin D production will have an impact on fundamental processes throughout the body (EPA 1986a). The potential impact is presented in Figure 2-7.

Some of the available evidence suggests a growth retardant effect of lead in children (Angle and Kuntzelman 1989; Lyngbye et al. 1987; Schwartz et al. 1986). These findings are supported by the results of independent prospective studies of prenatal effects on human development discussed in Section 2.2.1.5 on developmental toxicity and by numerous animal studies. However, several other studies have failed to identify a significant association between blood lead level and growth in children (Greene and Ernhart 1991; Sachs and Moel 1989). The mechanism of the effect of lead exposure on growth is unknown, but the finding of a suppressed release of thyrotropin-stimulating hormone (TSH) in response to thyrotropin-releasing hormone (TRH) in two young lead-intoxicated children suggests pituitary involvement (Huseman et al. 1987). In vitro studies with rat pituitary cells showed that lead inhibited the TRH-stimulated release of TSH in a dose-related manner (Huseman et al. 1987), supporting the conclusions drawn from the human data.

Immunological Effects. The effects on the immune system of young rats at blood lead levels of 29 μg/dL (Faith et al. 1979; Luster et al. 1978) and of mice at blood lead levels of 15–45 μg/dL (Hillam and Ozkan 1986) raise the concern that low-level exposure of humans to lead may have adverse effects on the immune system. The best available human data, while not fully adequate to address this issue, gave no indication of immune system effects in children with blood lead levels of ≥40 μg/dL (Reigart and Graber 1976) and a slight indication of adverse effects on the cellular component of the immune system in lead workers with blood lead levels that exceed 50 μg/dL (Alomran and Shleamoon 1988; Coscia et al. 1987; Ewers et al. 1982).

Neurological Effects. The data on neurobehavioral toxicity of exposure to lead suggest that children are more sensitive, as indicated by responses at lower blood lead levels, than are adult humans, and that animals are affected at roughly the same blood lead levels as are humans.

In humans, encephalopathy can occur at blood lead levels as low as 100–120 μg/dL in some adults (Kehoe 1961a, 1961b, 1961c; Smith et al. 1938) and at blood lead levels as low as 80–100 μg/dL in some children (EPA 1986a; NAS 1972). This condition can result in death or in permanent cognitive impairment, particularly in children. Furthermore, children with high blood lead levels (>80–100 μg/dL) and symptoms of lead poisoning, but no symptoms of acute encephalopathy, also have an increased incidence of lasting neurological and behavioral impairment (EPA 1986a).

Adults have been found to have overt neurological signs and symptoms and impairment on neurobehavioral tests at blood lead levels as low as 40–60 μg/dL (Baker et al. 1979, 1983; Campara et al. 1984; Haenninen et al. 1979; Williamson and Teo 1986; Zimmerman-Tansella et al. 1983). These blood lead levels are comparable to those at which other symptoms of lead poisoning, such as gastrointestinal symptoms, occur. Decreased NCVs have been observed in adults at blood lead levels as low as 30 μg/dL (Seppalainen et al. 1983). It is possible that impaired peripheral nerve function may have affected performance on some of the behavioral tests such as reaction time, grip strength, and eye-hand coordination.

In children with no symptoms of lead intoxication, the results have been inconsistent. Neurobehavioral impairment, including IQ deficits of approximately 5 points, has been associated with mean blood lead levels of approximately 50–70 μg/dL (de la Burde and Choate 1972; Rummo 1974; Rummo et al. 1979). IQ deficits of approximately 4 points have been associated with blood lead levels of 30–50 μg/dL (estimated from dentine lead values and other data by the EPA [1986a]) (Needleman et al. 1979). The highly significant inverse linear relationship between IQ and blood lead levels over the range of 6 to 46 μg/dL found by Hawk et al. (1986) and Schroeder and Hawk (1987) in black children of low socioeconomic status indicates that IQ decrements may occur without an evident threshold down to very low blood lead levels. A study of children of higher and less uniform socioeconomic status in Edinburgh, Scotland, also reported a significant inverse dose-effect relationship between blood lead level and cognitive ability, with no threshold evident from the mean blood level of 22.1 μg/dL in the highest lead group down to the mean blood lead level of 5.6 μg/dL in the lowest lead group (Fulton et al. 1987). Hence, the lack of threshold in the inverse relationship between blood lead level and cognitive function may pertain not only to low socioeconomic status children, but also to the general population of children. The data of Fulton et al. (1987) provide evidence of IQ deficits in children with lead exposure at blood lead levels <25 μg/dL (ATSDR 1988). Additional evidence associating neurobehavioral deficits with low blood lead levels of approximately 10–15 μg/dL or possibly lower can be found in studies of the effects of prenatal exposure, discussed in Section 2.2.4.5 on developmental toxicity. It should be noted that the effects of blood lead on IQ and other neurobehavioral scores are very small compared with the effects of other factors such as parent's IQ or vocabulary (Fulton et al. 1987; Pocock et al. 1987; Winneke et al. 1985a) but may have major implications for public health when considered on a population basis (Davis and Svendsgaard 1987; Grant and Davis 1989).

On the other hand, several studies have reported no association between neurobehavioral impairment and low levels of lead exposure. Cooney et al. (1989a) reported that blood lead levels of approximately 10 μg/dL had little or no effect on neurobehavioral development at age 4. Harvey et al. (1988) concluded that the effects of lead (mean blood lead = 13 μg/dL) were small and generally not significant. Likewise, Ernhart et al. (1988), Lansdown et al. (1986), McMichael et al. (1986), and Pocock et al. (1989) found no effect of lead on intelligence.

Hearing thresholds in children may be affected adversely by lead exposure at low blood lead levels (Robinson et al. 1985; Schwartz and Otto 1987). Robinson et al. (1985) reported that hearing thresholds increased linearly with maximum historical blood lead levels of 6.2-56.0 μg/dL. In the analysis by Schwartz and Otto (1987), the probability of elevated hearing thresholds increased significantly with increasing blood lead level across the entire range of blood lead levels studied (NHANES II data), from <4 to >50 μg/dL, with no apparent threshold. These two studies, however, may not have controlled for all relevant confounders.

Evidence of electrophysiological changes (altered slow-wave voltage during conditioning, changes in evoked potential measures and peripheral nerve conduction velocities) has been observed in children at low blood lead levels (15-30 μg/dL and possibly lower). Studies reporting these findings include EPA 1986a; Landrigan et al. 1976; Otto et al. 1981, 1982, 1985; Robinson et al. 1987; and Winneke et al. 1984.

Studies of animals have shown delays in reflex development in rats during early postnatal life at blood lead levels ≥59 μg/dL (Kishi et al. 1983) and alterations in visual evoked responses and decreased visual acuity in young rats at mean blood lead levels of 65 μg/dL (Cooper et al. 1980; Fox and Wright 1982; Fox et al. 1977; Impelman et al. 1982; Winneke 1980). Decreases in visual acuity persisted through 90 days of age even though exposure was terminated at 21 days of age.

Neurobehavioral effects, measured in various discrimination reversal and operant learning tests, were observed in rats. Blood lead levels as low as 15-20 μg/dL were associated with slower learning and higher rates of inappropriate responses (Cory-Slechta et al. 1985). Similar experiments in monkeys support the findings in rats and extend the dose-response relationship to even lower blood lead levels, comparable to those at which subtle effects are seen in human children. Monkeys given a soluble lead compound at 0.05 mg lead/kg/day orally from birth until neurobehavioral testing at 3-4, 6-7, and 9-10 years of age had peak and steady-state blood lead levels of 15.4 and 10.9 μg/dL and performed significantly less well in learning discrimination reversal and delayed alternation tasks than did controls (Gilbert and Rice 1987; Rice 1985a, 1985b). In addition, treatment of monkeys orally with lead for the first year of life so as to produce an average blood lead level of 32 μg/dL during that year resulted in neurobehavioral effects that persisted from termination of exposure at 1 year through 49-55 months of age, at which time blood lead levels had decreased to 5 μg/dL, virtually the same as control values (Bushnell and Bowman 1979b, 1979c).

Developmental Effects. Evidence from human studies that included anomalies as an end point (Ernhart et al. 1985, 1986; McMichael et al. 1986; Needleman et al. 1984) indicate no existence of an association between prenatal exposure to low levels of lead and the occurrence of major congenital anomalies. This conclusion is further supported by developmental toxicity studies conducted in rats and mice; these studies provide no evidence that lead compounds (acetate or nitrate) are teratogenic when exposure is by natural routes. Intravenous or intraperitoneal injection of lead compounds (acetate, chloride, or nitrate) into pregnant rats, mice, or hamsters, however, has produced malformations in several studies reviewed by EPA (1986a).

Studies evaluating exposure to low levels of lead and its influence upon birth weight and gestational age are more controversial. The earlier evidence for such effects has not been reproduced in the more recent studies by Factor-Litvak et al. (1991) and Greene and Ernhart (1991). A significant inverse association between prenatal maternal blood lead levels and birth weight was reported in the Cincinnati study (Bornschein et al. 1989; Dietrich et al. 1986, 1987a). An earlier study showed that the percentage of small-for-gestational-age infants increased with increasing cord blood lead, although the trend was not quite statistically significant (Bellinger et al. 1984). Significant direct associations between maternal and cord blood lead levels and birth weight were reported by McMichael et al. (1986). On the other hand, no association has been observed between maternal or cord blood levels and birth weight in several other studies (Ernhart et al. 1985, 1986; Factor-Litvak et al. 1991; Greene and Ernhart, 1991; Moore et al. 1982; Needleman et al. 1984).

Evidence from some of the above studies also indicates that gestational age may be reduced as prenatal lead exposure increases, even at blood lead levels below 15 μg/dL (EPA 1986a). Significant negative correlations between maternal or cord blood lead levels and gestational age were reported by Dietrich et al. (1986, 1987a), McMichael et al. (1986); and Moore et al. (1982). Based on parameter estimates of Dietrich et al. (1986), the reduction in gestational age was 0.6 week per natural log unit of blood lead increase (EPA 1986a). Based on risk estimates of McMichael et al. (1986), the risk of preterm delivery increases by at least fourfold as either cord blood or maternal blood lead level at delivery increases from $\leq$8 to >14 μg/dL. However, other investigators did not find a significant relationship between maternal or cord blood lead level and gestational age (Bellinger et al. 1984; Factor-Litvak et al. 1991; Needleman et al. 1984).

The evidence from studies showing neurobehavioral effects following prenatal exposure to low levels of lead suggests that neurobehavioral deficits are associated with prenatal internal exposure levels, as indicated by maternal or cord blood lead concentrations, of approximately 10–15 μg/dL, and possibly even lower (ATSDR 1988; Davis and Svendsgaard 1987; EPA 1986a; Grant and Davis 1989). Although a 2–8-point decline in MDI score for an individual child may not be clinically significant, a 4-point downward shift in a normal distribution of MDI scores of a population of children would result in 50% more children scoring below 80, a consequence of great concern to public health (Davis and Svendsgaard 1987; Grant and Davis 1989). Additional evidence of an association between relatively low blood lead levels and neurobehavioral effects in children is reported in Section 2.2.1.4.

Some studies demonstrating neurobehavioral and developmental effects discussed in this section on developmental toxicity as well as in the previous section on neurobehavioral toxicity have been criticized for methodological flaws, including handling of cofactors (EPA 1986a; Ernhart 1988). ATSDR (1988) and EPA (1986a) have taken such criticisms into account, and have concluded that the findings associating relatively low blood lead levels with neurobehavioral and developmental effects in children are nonetheless cause for concern. It should be noted that some studies, demonstrating no such association, have also been criticized for methodological flaws that bias towards Type II (false negative) errors (Needleman 1987b; Needleman and Bellinger 1989). Although no single study associating low blood lead levels with reduced cognitive performance in children is definitive, a meta analysis of 13 studies providing data on an inverse relationship between blood lead and children's IQs concluded that the joint probability of obtaining the reported results was less than 3 in a billion (Needleman 1987b; Needleman and Bellinger 1989).

Animal studies also provide evidence of neurobehavioral toxicity of prenatal exposure to low levels of lead. In an extensive review of the literature, Davis et al. (1990) discussed similarities between human effects and those in animals. The authors concluded that qualitatively ". . . the greatest similarities between human and animal effects involve cognitive and relatively complex behavioral processes such as learning." They further reported that quantitative relationships for blood lead levels across species that cause developmental neurobehavioral effects are 10–15 μg/dL in children, <15 μg/dL in primates, and <20 μg/dL in rodents.

In contrast to animal studies of prenatal exposure, animal studies of postnatal exposure show effects at blood lead levels similar to those associated with effects in humans.

Reproductive Effects. There is sufficient qualitative evidence to support the conclusion that at high occupational exposure levels lead has significant adverse effects on human reproduction, including increased incidences of spontaneous abortion, miscarriages, and stillbirths. The mechanisms responsible for these effects are unknown at this time, but many factors may contribute to these results. These factors include indirect effects of lead on maternal nutrition or hormonal status before and during pregnancy to more direct gametogenic effects that could affect parental fertility in either sex. The available data do not permit any estimate of effect levels in women, although two recent studies found no effect on the rate of spontaneous abortions at blood lead levels of 10 μg/dL. Only a tentative conclusion can be drawn that chronic exposure at blood lead levels of 40-50 μg/dL in men may cause effects on sperm or the testes.

Genotoxic Effects. Evaluation of the genotoxicity of lead in humans has focused on in vitro studies of structural chromosomal aberrations and sister chromatid exchange in cultures of lymphocytes taken from healthy individuals (Table 2-6), and evaluations of lymphocytes from occupationally or environmentally exposed persons (Table 2-7). Results of studies with human lymphocyte cultures exposed in vitro to lead acetate were nearly equally divided between positive (Beek and Obe 1974; Niebuhr and Wulf 1984) and negative (Beek and Obe 1975; Deknudt and Deminatti 1978; Gasiorek and Bauchinger 1981; Schmid et al. 1972).

Maternal and fetal chromosomal aberrations were observed in mice following prenatal exposure to subembryotoxic doses of lead nitrate (Nayak et al. 1989a). Pregnant Swiss Webster mice were given intravenous doses of lead nitrate at levels of 12.5, 25, 50, and 75 mg/kg body weight on the 9th day of gestation. On day 18, the animals were killed, and maternal bone marrow cells and fetal liver cells were examined for chromosomal aberrations. Low levels of constitutive changes mostly in the form of deletions were seen at all doses administered in both maternal and fetal cells. No statistical analyses were presented. These data indicate that prenatal exposure to lead may induce genotoxic changes in the fetus.

A single intracardiac dose of 40 μg/g body weight lead acetate induced a 25-fold increase in mitosis of mouse liver cells 5 hours after injection (Choie and Richter 1978). Results were mixed for various manifestations of genotoxicity or cell cycle disruptions in several experiments with lead acetate in mammals (Bruce and Heddle 1979; Deknudt and Gerber 1979; Deknudt et al. 1977; Jacquet and Tachon 1981; Jacquet et al. 1977; Muro and Goyer 1969; Tachi et al. 1985; Willems et al. 1982).

Acute intraperitoneal exposure to 25 mg lead/kg resulted in no increase in the number of micronuclei in bone marrow polychromatic erythrocytes in mice (Jacquet et al. 1977). Lead acetate administered intraperitoneally to Sprague-Dawley rats caused an increase in the percentage of aberrant bone marrow cells in female, but not male rats. The aberrations were primarily chromatid gaps, although there was no dose dependency across the four dose points used (Tachi et al. 1985).

Several genotoxic end points were assayed in male rabbits after subcutaneous injection of doses of 0, 0.25, and 0.50 mg lead acetate/kg body weight three times a week for 14 weeks. No treatment-related effects were seen in sperm count, morphologic abnormalities of sperm, histopathology of the testes, or on the number of sister chromatid exchanges in lymphocytes or the relative number of micronuclei in bone marrow erythrocytes (Willems et al. 1982). Tests for gene mutations, DNA modification, and recombinations in various microorganisms (See Table 2-7) using lead acetate (Bruce and Heddle 1979; Dunkel et al. 1984; Nishioka 1975; Rosenkranz and Poirier 1979; Simmon 1979a, 1979b; Simmon et al. 1979), lead nitrate (Kharab and Singh 1985), and lead chloride (Fukunaga et al. 1982; Nishioka 1975) were consistently negative with or without metabolic activation. Lead chloride was shown to be mutagenic in Salmonella typhimurium strain TA102 without S9 activation; it was nonmutagenic in three other strains with and

TABLE 2-6. Genotoxicity of Lead In Vitro

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Salmonella typhimurium (reverse mutation); Escherichia coli (forward mutation, DNA modification); Saccharomyces cerevisiae (reverse mutation); Bacillus subtilis (rec assay)	Gene mutation or DNA modification	–	–	Bruce and Heddle 1979; Dunkel et al. 1984; Fukunaga et al. 1982; Kharab and Singh 1985; Nestmann et al. 1979; Nishioka 1975; Rosenkranz and Poirier 1979; Simmon 1979b
S. cerevisiae	Gene conversion or mitotic recombination	–	–	Fukunaga et al. 1982; Kharab and Singh 1985; Nestmann et al. 1979; Simmon 1979a
E. coli RNA polymerase or Avian myetoblastosis DNA polymerase	RNA or DNA synthesis	NA	+	Hoffman and Niyogi 1977; Sirover and Loeb 1976
Chinese hamster ovary cells; Syrian hamster embryo cells	Chromosomal aberration, DNA repair, mitotic disturbance	NA	+	Bauchinger and Schmid 1972; Costa et al. 1982; Robison et al. 1984
Human lymphocyte cultures	Structural chromosomal aberration	NA	+	Beek and Obe 1974
			–	Deknudt and Deminatti 1978
			–	Gasiorek and Bauchinger 1981; Schmid et al. 1972
Human lymphocyte cultures	Sister chromatid exchange	NA	–	Beek and Obe 1975
			+	Niebuhr and Wulf 1984

– = negative result; + = positive result; DNA = deoxyribonucleic acid; NA = not applicable; RNA = ribonucleic acid

TABLE 2-7. Genotoxicity of Lead *In Vivo*

Species (test system)	End point	Results	Reference
Drosophila melanogaster	Chromosome loss or nondisjunction	–	Ramel and Magnusson 1979
Mouse bone marrow, rat bone marrow, mouse leukocyte, monkey lymphocyte, rabbit	Structural chromosomal aberrations or gaps, micronucleus formation; unscheduled DNA synthesis, sister chromatid exchange	–/+	Bruce and Heddle 1979; Deknudt and Gerber 1979
		+	Deknudt et al. 1977
		+	Jacquet and Tachon 1981
		–	Jacquet et al. 1977
		–	Muro and Goyer 1969
		+	Tachi et al. 1985
		–	Willems et al. 1982
Human, occupational	Chromosomal aberration	+	Al-Hakkak et al. 1986
		–	Bauchinger et al. 1977
		+	Forni et al. 1976
		–	Mäki-Paakkanen et al. 1981
		+	Nordenson et al. 1978
		–	O'Riordan and Evans 1974
		–/+	Schwanitz et al. 1970, 1975
		+	Huang et al. 1988b
		–	Schmid et al. 1972
Human, occupational exposure	Sister chromatid exchange	–	Grandjean et al. 1983
		–	Mäki-Paakkanen et al. 1981
Human, environmentally exposed children		–	Dalpra et al. 1983
		–	Leal-Garza et al. 1986
		–	Huang et al. 1988b
Human	Effects on cell division	+	Bulsma and DeFrance 1976
		+	Forni et al. 1976
		+	Sarto et al. 1978
		+	Schwanitz et al. 1970

– = negative result; + = positive result; –/+ = inconclusive result; DNA = deoxyribonucleic acid without activation (Wong 1988). A positive response was observed by Nestmann et al. (1979) for lead chromate, but further testing clarified that the positive response was associated with the chromate rather than the lead moiety. Lead chloride has been shown to inhibit both RNA (Hoffman and Niyogi 1977) and DNA (Sirover and Loeb 1976) synthesis.

In mammalian test systems in vitro (Syrian or Chinese hamster cells), lead acetate gave conflicting results for structural chromosomal aberrations (Bauchinger and Schmid 1972; Robison et al. 1984). Lead acetate increased the frequency of DNA repair (Robison et al. 1984), the frequency of achromatic lesions and gaps (Bauchinger and Schmid 1972), and both lead acetate (Bauchinger and Schmid 1972) and lead sulfate (Costa et al. 1982) interfered with normal mitotic division. Both lead sulfide and lead nitrate were mutagenic at the hypoxanthine guanine phosphoribosyl transferase (HPRT) locus in Chinese hamster V79 cells (Zelikoff et al. 1988). Because these investigators failed to demonstrate either sister chromatid exchange induction or DNA single-strand breaks following treatment with either lead compound, they propose an indirect mechanism of genotoxicity probably involving DNA repair enzymes. A series of experiments with lead acetate alone and lead acetate in conjunction with ultraviolet radiation indicate that the mechanism of genotoxicity of lead ions may indeed be an indirect one (Hartwig et al. 1990). Lead acetate alone did not induce DNA-strand breaks in HeLa cells or mutations at the HPRT locus, nor did it increase sister chromatid exchange frequency in V79 Chinese hamster cells. However, for all end points tested, lead ions interfered with the processing of UV-induced DNA damage, thus increasing the frequency of the end points measured. These authors suggested the possibility of interference with repair enzymes such as polymerase or ligase, or else interaction with calcium-regulated processes. An interaction with calcium-regulated processes, such as those modified by calmodulin, would be consistent with other observed interactions with calcium levels (Deknudt at al. 1977). Lead is also known to form complexes with amine and carboxyl groups of proteins, which in turn can lead to enzyme inactivation (Bota et al. 1982).

Cancer. The information available on the carcinogenicity of lead in occupationally exposed humans is limited in its usefulness because the actual compound(s) of lead, the route(s) of exposure, and levels of lead to which the workers were exposed were not reported. Furthermore, concurrent exposure to other chemicals, including arsenic, probably occurred, particularly in lead smelters, and confounding variables, such as smoking, were often not accounted for. Therefore, the data currently available do not permit an assessment of the potential carcinogenic risk of lead in humans.

According to a recent EPA (1988b) assessment, the available epidemiological studies lacked quantitative exposure data for lead and for possible confounding exposures (e.g., arsenic, smoking), cancer excesses in the lung and stomach of lead-exposed workers were relatively small, dose-response relationships were not demonstrated in any study, and no consistency of site was observed among the various studies. EPA (1988b) concluded that the human data are inadequate to refute or demonstrate the potential carcinogenicity of lead exposure.

The available data on the carcinogenicity of lead following ingestion by laboratory animals indicate that lead is carcinogenic, and that the most common tumor response is renal tumors (Azar et al. 1973; Koller et al. 1985; Van Esch and Kroes 1969). Administration of lead compounds by the parenteral route has given similar results. Lead subacetate was positive at high dosages in the strain A mouse lung adenoma bioassay (Poirier et al. 1984; Stoner et al. 1976), but the positive response was blocked by simultaneous administration of calcium or magnesium acetate (Poirier et al. 1984). Subcutaneous administration of lead phosphate to rats was associated with high incidence of renal tumors (Balo et al. 1965; Zollinger 1953). Lead acetate was positive in cell transformation tests in Syrian hamster embryo cells (Dunkel et al. 1981; Pienta et al. 1977) and in MLV-infected rat embryo cells (Dunkel et al. 1981), and enhanced simian adenovirus (SA-7) transformation of Syrian hamster embryo cells (Casto et al. 1979). Lead oxide also enhanced SA-7 transformation of Syrian hamster embryo cells (Casto et al. 1979).

The extremely high cumulative doses of lead used in these studies are difficult to extrapolate to low-level exposure in humans, and thus do not provide a sufficient basis for quantitative risk assessment (see discussion below). In addition, it is possible that the high doses required to induce renal tumors may themselves have produced a carcinogenic effect that was independent of any direct effect of lead as a result of nonspecific tissue damage. Furthermore, the relevance of male rat kidney tumors induced by some chemicals to humans has been questioned (EPA 1991c). It is not known whether the mechanism by which lead induces tumors in the rat kidney involves the same or similar species-specific proteins (α_{2u}-globulin) identified in the recent studies of other substances, such as unleaded gasoline (see Section 2.9.3 for a discussion of on-going research designed to answer this question). Other deficiencies associated with these animal studies that limit their usefulness with respect to risk assessment include the fact that they are generally over 10 years old with small group sizes and poor reporting of results.

EPA (1988b) concluded that the animal data are sufficient to demonstrate that lead and (inorganic lead) compounds, particularly soluble lead salts, are carcinogenic to animals. Although dose-response data are available from animal studies, EPA (1988b) recommended that a numerical estimate of cancer potency or risk based on such data should not be used because of the uncertainties, some of which may be unique to lead, involved in such an extrapolation. Current knowledge of the pharmacokinetics of lead indicates that an estimate derived by standard methods would not adequately delineate the potential risk (IRIS 1990). EPA (IRIS 1990) assigned lead and (inorganic) lead compounds a classification of B2, probable human carcinogen.

The International Agency for Research on Cancer (IARC 1987) concluded that the evidence for carcinogenicity of lead and inorganic lead compounds was inadequate in humans and sufficient in animals. IARC (1987) classified lead and inorganic lead compounds in IARC Group 2B, possible human carcinogen.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecules or cells that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluids or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to lead are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by lead are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "Populations That Are Unusually Susceptible."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Lead

Biomarkers of exposure for inorganic and organic forms of lead are usually the measurement of total lead levels in tissues or fluids. Tetraalkyl lead compounds may also be measured in the breath.

Measurement of blood lead concentration is the most widely used biomarker of lead exposure. A blood lead level greater than 10 µg/dL indicates that excessive lead exposure may be occurring (CDC 1991). The half-life of lead in human blood is 28–36 days (Griffin et al. 1975b; Rabinowitz et al. 1976); thus, levels in blood reflect relatively recent exposure (Lyngbye et al. 1990b). Nevertheless, because lead cycles between the blood and bone, a single blood lead determination cannot distinguish between low-level intermediate or chronic exposure and high-level acute exposure. Both types of exposure could result in the same blood level because of recycling from bone. Therefore, blood lead levels cannot serve as exact measures of lead exposure or the total body lead burden because of the intervening processes of transfer, mobilization, and storage among the different body compartments. However, the relationship of lead levels in air, food, and water to levels in blood is not well-defined, but may be described as curvilinear, such that the increase in blood concentration is less at high exposure levels than at low exposure levels (EPA 1986a; Manton and Cook 1984). This behavior may be attributed to changes in tissue lead kinetics, reduced lead absorption, or increased excretion, such that blood lead may be an imperfect measure of tissue lead burdens and of changes in tissue levels in relation to changes in external exposure (EPA 1986a). Despite the limitations of blood levels in indexing tissue burden and exposure changes, this parameter still remains the one readily accessible measure that can demonstrate in a relative way the relationship of various effects to increases in exposure. The biological exposure index (BEI) for lead in blood of exposed workers is 50 µg/dL (ACGIH 1990). This blood level represents the threshold for effects seen in at least some adults; therefore, because of individual variations in sensitivity, many people may not experience the stated effect until much higher blood levels are reached. Furthermore, instability of blood lead levels have been reported to occur in infants in which the average increase in blood lead from birth to 2 years of age was 5 µg/dL while levels for older children were found to be more stable (Rabinowitz et al. 1984). The influence of age, sex, and smoking may also be potential confounders on the interpretation of blood lead measurements (Rabinowitz et al. 1976; Somashekaraiah et al. 1990; Watanabe et al. 1987).

Urinary lead levels have also been used to measure current exposure (Robinson 1974) but they are of questionable value as biomarkers of exposure because of the relatively low and fluctuating lead levels excreted in the urine (ACGIH 1986; Ibels and Pollock 1986; Jensen 1984). On the contrary, the determination of urinary lead following chelation with calcium disodium EDTA, which mobilizes tissue lead and produces increased urinary excretion of lead, is presumed to be indicative of an elevated body burden of lead (Cory-Slechta et al. 1987; Ibels and Pollock 1986; Janin et al. 1985), but this test has not been empirically validated. Children whose blood lead levels are ≥45 μg/dL should not receive a provocative chelation test; they should be referred for appropriate chelation therapy immediately (CDC 1991). Furthermore, recent work by Cory-Slechta et al. (1987) indicates that diagnostic calcium disodium EDTA chelation may increase the levels of lead in the liver and brain, raising serious concern about continued use of calcium disodium EDTA as a diagnostic tool in children.

Because it can accumulate lead, the tooth has been considered a potential biomarker for measuring chronic exposure to lead (Steenhout and Pourtois 1987). An association between blood lead and tooth lead was reported with increasing age in children (Rabinowitz et al. 1989). Since teeth can store up lead to the time of shedding or extraction, levels of lead in shed teeth may be valuable in assessing exposure at remote time points, or cumulative chronic-duration exposure (EPA 1986a). The determination of lead in shed teeth, however, is retrospective and of little value in monitoring current exposure. Thus, the measurement of lead in teeth in situ may be a more valuable indicator of cumulative lead exposure (EPA 1986a). Dentine appears to be the best material in the tooth to use to estimate lead exposure because the lead content in dentine is from the blood stream whereas lead measured in enamel may be influenced by external lead levels (Purchase and Fergusson 1986).

Another indicator of current exposure to lead is hair because it offers the advantage of being a noninvasive stable medium. It has been used as an indicator for intermediate exposure (2 months) in children (Wilhelm et al. 1989). However, artificial hair treatment (i.e., dyeing, bleaching, permanents) can invalidate metal analysis of hair (Wilhelm et al. 1989), and external surface contamination problems are such that it is difficult to differentiate between externally and internally deposited lead (EPA 1986a).

In vivo tibial X-ray fluorescence (XRF), which measures bone lead content, provides a noninvasive means of estimating cumulative lead absorption (Batuman et al. 1989; Hu et al. 1989, 1990, 1991; Wedeen 1988, 1990). While the biomarkers discussed above are representative only of current lead exposure (i.e., blood lead levels), bone lead (where 90% of the total body burden of lead is found) represents the net result of absorption and excretion of lead over time. It has been reported that low-level lead exposure results in tibial lead concentrations of about 7.5 ppm wet weight in adults, which corresponds to blood lead levels of about 10 μg/dL and EDTA lead mobilization tests averaging up to 400 μg lead-chelate per day (Wedeen 1990). For individuals exposed to moderate levels of lead (i.e., those living near a stationary source of lead), the bone concentration of lead is found to be around 20 ppm, which corresponds to a blood lead level of ≥30 μg/dL (Wedeen 1990). However, one limitation to this method of estimating exposure to lead is that it is difficult to measure bone lead concentrations <10 ppm reliably (Wedeen 1988). See Chapter 6 for more details regarding this method.

Physiological changes that are known to implicate lead exposure may also be used as biomarkers of exposure. Generally, blood lead levels are determined concurrently with these physiological biomarkers. Interference with heme synthesis following lead exposure can lead to a reduction of hemoglobin concentration in blood (Bernard and Becker 1988) and an increase in urinary coproporphyrin (EPA 1986a). Measurement of specific enzymes or intermediates in the heme synthesis pathway can suggest that lead exposure has occurred. ALAD activity measured in erythrocytes may be associated with recent exposure to lead because, as with blood lead levels, there is not a large time lag between exposure and decreased activity of this enzyme in workers entering occupational lead exposure for the first time (Tola et al. 1973). In addition, a negative correlation between ALAD activity and blood lead levels of 5-95 μg/dL was observed by Hernberg et al. (1970). ALA, the intermediate that accumulates from decreased ALAD, can be detected in the urine when blood lead levels are 35 μg/dL in adults and 25–75 μg/dL in children (NAS 1970; Roels and Lauwerys 1987); thus, ALA in urine is not considered as sensitive a measure of current lead exposure as ALAD activity (Hernberg et al. 1970). Inhibition of ferrochelatase in the heme pathway causes accumulation of protoporphyrin in erythrocytes (CDC 1985). The concentration of EP rises above background at blood lead levels of 25–30 μg/dL (CDC 1985); there is a positive correlation between blood lead levels and EP (CDC 1985; Hernberg et al. 1970; Tola et al. 1973). Determination of EP in blood is an indicator of past chronic exposure since elevated EP reflects average blood levels for the past 4 months (ACGIH 1986; Janin et al. 1985). Therefore, EP is found to be better for population investigations than for routine occupational exposure (Haeger-Aronsen et al. 1971). However, other diseases or conditions such as porphyria, liver cirrhosis, iron deficiency, age, and alcoholism may also produce similar effects on heme synthesis (Somashekaraiah et al. 1990). Therefore, blood lead concentration is the best biomarker of exposure.

It was reported that the reduction in the serum 1,25-dihydroxyvitamin D concentration was a sensitive index of increased lead absorption or lead levels in the blood (Rosen et al. 1980). Lead inhibits the formation of this active metabolite of vitamin D, which occurs in bone mineral metabolism (EPA 1986a; Landrigan 1989). Children with blood concentrations of 12–120 μg/dL lead showed decreased serum 1,25-dihydroxyvitamin D concentrations comparable to those found in patients with hypoparathyroidism, uremia, and metabolic bone disease (Mahaffey et al. 1982; Rosen et al. 1980). This biomarker is clearly not specific for lead exposure since several diseases can also influence this measurement.

In summary, several indices in blood and body tissues are available to serve as biomarkers for lead exposure. Blood lead levels are the easiest and most widely used index of lead exposure. A blood lead level >10 μg/dL is considered excessive. Since the half-life of lead in blood is 28–36 days, blood lead levels generally reflect relatively recent exposure. However, because of continuous mobilization and recycling of lead from soft tissue and bone, blood lead levels cannot be used to distinguish between low-level intermediate or chronic exposure and high-level acute exposure. A blood lead level of 50 μg/dL has been determined to be an approximate threshold for the expression of lead toxicity in exposed workers.

Urinary lead is generally not a useful biomarker to estimate general population (i.e., low-level) exposure to lead. However, elevated urinary lead-chelate complexes resulting from the EDTA mobilization test provide a good means to assess increased lead body burden.

Tooth lead is useful to assess exposures that occurred remotely in time and cumulative chronic exposure. Measurement of lead in teeth is not useful to assess recent exposure. Hair lead has also been used to assess intermediate or chronic exposures. In vivo tibial bone lead XRF provides a good estimate of cumulative lead exposure with the advantage that it represents the net result of lead absorption/excretion in bone over time. For low-level exposure, tibial lead is about 7.5 ppm wet weight, which correlates with blood lead levels of 10 μg/dL, and moderate exposure results in tibial lead levels of 20 ppm, which correlates with blood lead levels of 30 μg/dL. One disadvantage of tibial XRF is that it is not as reliable at levels less than 10 ppm.

ALAD in blood is a sensitive indicator of recent exposure to lead. Urinary ALA becomes elevated at blood lead levels ≥50 μg/dL, and is not as sensitive an indicator as ALAD. EP becomes elevated at blood lead levels of 25–30 μg/dL and are a good indicator of past chronic exposure to lead.

With any of these biomarkers of exposure, it is not possible to predict how long they remain elevated after exposure has ceased. Refer to Section 2.3 for additional information on potential biomarkers of lead exposure.

2.5.2 Biomarkers Used to Characterize Effects Caused by Lead

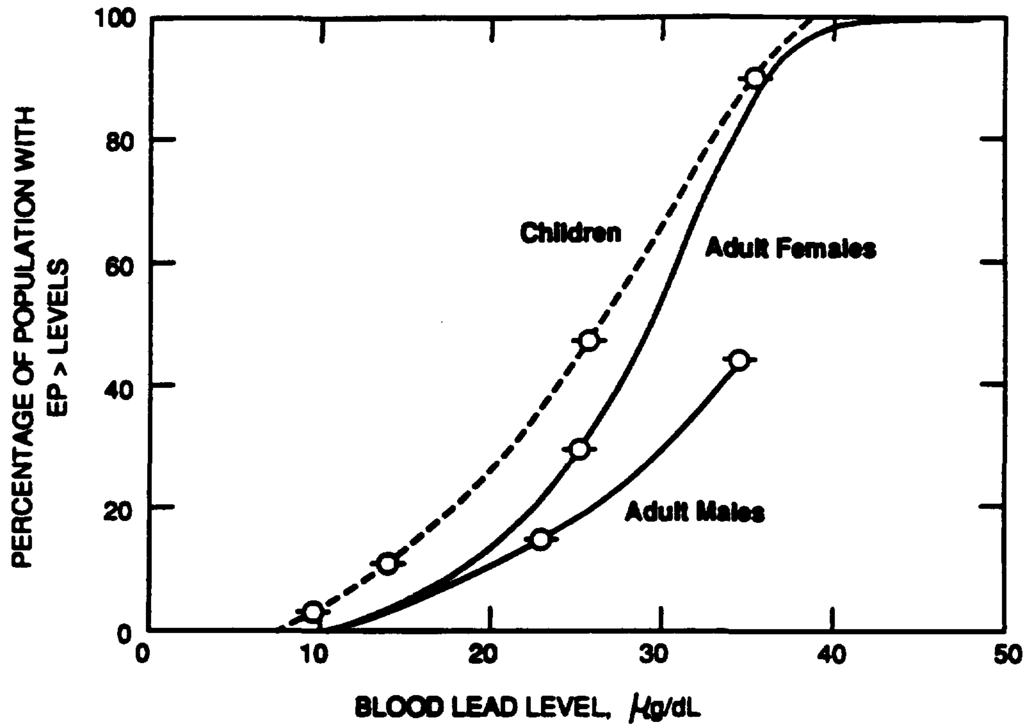
One of the most sensitive effects of lead exposure is the inhibition of the heme biosynthesis pathway, which is necessary for the production of red blood cells. Hematologic tests such as hemoglobin concentration may suggest toxicity, but this is very nonspecific (Bernard and Becker 1988). Measurements of FEP and ZPP, the form of EP in red blood cells, reflect essentially the same compound and can both be used as biomarkers of effect (CDC 1985). An elevated EP level is one of the earliest and most reliable indicators of impairment of heme biosynthesis and reflects average lead levels at the site of erythropoiesis over the previous 4 months (Janin et al. 1985). Lead toxicity is generally considered to be present when a blood level of ≥10 μg/dL is associated with an EP level of ≥35 μg/dL (CDC 1991; Somashekaraiah et al. 1990). This effect is detectable in circulating erythrocytes only after a lag time reflecting maturation in which the entire population of red blood cells has turned over (i.e., 120 days) (EPA 1986a; Moore and Goldberg 1985). Likewise, elevated erythrocyte protoporphyrin can reflect iron deficiency, sickle cell anemia, and hyperbilirubinemia (jaundice). Therefore, reliance on EP levels alone for initial screening could result in an appreciable number of false positive cases (CDC 1985; Mahaffey and Annest 1986; Marcus and Schwartz 1987). A limitation of measuring porphyrin accumulation is that porphyrin is labile because of to photochemical decomposition; thus, assay samples must be protected from light. A dose-response curve for EP as a function of blood lead level is depicted in Figure 2-8.

ALAD, an enzyme occurring early in the heme pathway, is also considered a sensitive indicator of lead effect (Hernberg et al. 1970; Morris et al. 1988; Somashekaraiah et al. 1990; Tola et al. 1973). Because there is no well-defined blood lead threshold at which inhibition of ALAD does not occur, it allows measurement of the effect on the general population at environmental lead levels and does not require high exposure levels as with occupational workers (Hernberg et al. 1970). However, ALAD activity may also be decreased with other diseases or conditions such as porphyria, liver cirrhosis, and alcoholism (Somashekaraiah et al. 1990).

Another potential biomarker for hematologic effects of lead is the observation of basophilic stippling and premature erythrocyte hemolysis (Paglia et al. 1975; 1977). Lead can impair the activity of pyrimidine 5'-nucleotidase, resulting in a corresponding increase in pyrimidine nucleotides in red blood cells, which leads to a deficiency in maturing erythroid elements and thus, decreased red blood cells. However, this effect is nonspecific; it is encountered with benzene and arsenic poisoning (Smith et al. 1938) and in a genetically-induced enzyme-deficiency syndrome (Paglia et al. 1975; 1977). Furthermore, since basophilic stippling is not universally found in chronic lead poisoning, it is relatively insensitive to lesser degrees of lead toxicity (CDC 1985).

One of the most sensitive systems affected by lead exposure is the nervous system. Encephalopathy is characterized by symptoms such as coma, seizures, ataxia, apathy, bizarre behavior, and incoordination (CDC 1985). Children are more sensitive to neurological changes. In children, encephalopathy has been associated with blood lead levels as low as 70 μg/dL (CDC 1985). The most sensitive peripheral index of neurotoxicity of lead is reported to be slowed conduction in small motor fibers of the ulnar nerve in workers with 30–40 μg/dL lead in blood (Landrigan 1989). Other potential biomarkers of lead suggested for neurotoxicity in workers are neurological and behavioral tests, as well as cognitive and visual sensory

FIGURE 2-8. Dose-Response Curve for Erythrocyte Protoporphyrin (EP) as a Function of Blood Level in Subpopulations*



* Derived from Roels et al. 1976

function tests (Williamson and Teo 1986). However, poor performance in these tests is not specific to lead toxicity.

The kidneys are affected by high-level, chronic exposure to lead (Landrigan 1989). Increases in BUN or serum creatinine are clinical manifestations of kidney damage (Landrigan 1989), but they do not reflect early loss of renal function and are nonspecific (Bernard and Becker 1988). Intranuclear inclusion bodies in the lining cells of the proximal tubules are reported to be the most characteristic feature of early nephropathy (Bernard and Becker 1988). These lead inclusion bodies disappear with appropriate chelation and shed into the urine. Thus, EDTA lead mobilization test may be the best test for diagnosing persons at risk of chronic lead nephropathy.

2.6 INTERACTIONS WITH OTHER CHEMICALS

The toxicokinetic and toxicological behavior of lead can be affected by interactions with essential elements and nutrients. In humans, the interactive behavior of lead and various nutritional factors is appropriately viewed as particularly significant for children, since this age group is not only particularly sensitive to the effects of lead, but also experiences the greatest changes in relative nutrient status. Nutritional deficiencies are especially pronounced in children of lower socioeconomic status; however, children of all socioeconomic strata are affected.

Available data from a number of reports document the association of lead absorption with suboptimal nutritional status. In infants and children 1–6 years of age, lead retention (as measured by blood lead content) was inversely correlated with calcium intake, expressed either as a percentage of total or on a weight basis (Johnson and Tenuta 1979; Sorrell et al. 1977; Ziegler et al. 1978). Dietary intakes of calcium and vitamin D were significantly ($p<0.001$) lower in children with blood levels >60 μg/dL (Johnson and Tenuta 1979). The gastrointestinal uptake of ^{203}Pb was monitored in eight adult subjects as a function of dietary calcium and phosphorus intakes (Heard and Chamberlain 1982). The label absorption rate was 63% without supplementation of these minerals in fasting subjects, compared with 10% in subjects supplemented with 200 mg calcium plus 140 mg phosphorus, the amounts present in an average meal. Calcium and phosphorus alone reduced lead uptake by a factor of 1.3 and 1.2, respectively; both together yielded a reduction factor of 6. Copper, iron, and zinc have also been postulated to affect lead absorption (Klauder and Petering 1975).

Children with elevated blood lead (12–120 μg/dL) were found to have significantly lower serum concentrations of the vitamin D metabolite 1,25-dihydroxyvitamin D compared with age-matched controls ($p<0.001$), and showed a negative correlation of serum 1,25-dihydroxyvitamin D with lead over the range of blood lead levels measured (Mahaffey et al. 1982; Rosen et al. 1980).

Zinc appears to be an important element in the ALAD system and may play a protective role in lead intoxication by reversing the enzyme-inhibiting effects of lead. Children with high blood lead levels (50–67 μg/dL) were reported to consume less zinc than children with lower blood levels (12–29 μg/dL) (Johnson and Tenuta 1979). In a group of 13 children, Markowitz and Rosen (1981) reported that the mean serum zinc levels in children with plumbism were significantly below the values seen in normal children; chelation therapy reduced the mean level even further. An inverse relationship between ALA in urine and the amount of chelatable or systemically active zinc was reported in 66 children challenged with EDTA and having blood lead levels ranging from 45–60 μg/dL (Chisolm 1981). Zinc sulfate administration to a lead-intoxicated man following calcium disodium EDTA therapy restored the erythrocyte

ALAD activity that was inhibited by lead (Thomasino et al. 1977). This suggests that zinc is an important requirement in the ALAD system.

Forty-three children with elevated blood lead (>30 μg/dL) and EP (>35 μg/dL) had an increased prevalence of iron deficiency as these two parameters increased (Yip et al. 1981). An inverse relationship between chelatable iron and chelatable body lead levels as indexed by urinary ALA levels has been demonstrated in 66 children with elevated blood lead (Chisolm 1981). Another study reported that the lead absorption rate was 2 to 3 times greater in iron-deficient adults compared to subjects who were iron replete (Watson et al. 1980). Daily nutritional intake of dietary fiber, iron, and thiamine were negatively correlated with blood lead levels in male workers occupationally exposed to lead in a steel factory (Ito et al. 1987). An in vitro study demonstrated that cadmium and zinc have an antagonistic effect on the inhibitory effects of lead on human ALAD activity (Davis and Avram 1978). Cadmium was 40–100 times more potent than zinc in activating ALAD. Furthermore, the combined effects of cadmium and lead in tissue resulted in an additively increased risk of mortality related to cardiac failure in humans with significant relation to age in 80% of the cases (Voors et al. 1982).

Reports of lead-nutrient interactions in experimental animals have generally described such relationships in terms of a single nutrient, using relative absorption or tissue retention in the animal to index the effect. Most of the data are concerned with the impact of dietary levels of calcium, iron, phosphorus, and vitamin D. These interaction studies are summarized in Table 2-8.

Lead has also been found to interact with a number of other metals in the bodies of animals with resultant synergistic, additive, or antagonistic effects.

Animals on low-calcium diets exhibit increased susceptibility to lead as a consequence of increased lead retention associated with decreased renal excretion of lead (Barton et al. 1978a; Goyer 1986). A low-calcium diet has been shown to promote genetic damage by lead (Deknudt and Gerber 1979). Lead administered to mice in combination with a low-calcium diet produced an excess of chromosomal aberrations compared with low-calcium controls fed no lead or with mice administered lead on a normal-calcium diet. In addition, a significantly increased frequency of severe chromosomal abnormalities (dicentrics, rings, translocations, and exchanges) was found in monkeys given lead in conjunction with a low-calcium diet compared with a group given as much lead but on a normal diet (Deknudt et al. 1977). Calcium and magnesium prevented an increase in lung adenoma formation in mice administered lead subacetate (Poirier et al. 1984). It has been postulated that calcium and lead compete for similar binding sites on intestinal mucosal proteins, which are important in the absorptive process (Barton et al. 1978a).

It has also been demonstrated in animals that lead blocks the intestinal responses to vitamin D and its metabolites (Smith et al. 1981). Dietary concentrations of lead in combination with a low phosphorus or a low calcium diet administered to rats suppressed plasma levels of the vitamin D metabolite, 1,25-dihydroxycholecaliferol, while dietary intakes rich in calcium and phosphorus protected against this effect (Smith et al. 1981). Thus, animals fed a diet high in calcium or phosphorus appear to be less susceptible to the effects of lead, because of hindered tissue accumulation of lead as calcium and phosphorus interfere with gastrointestinal absorption of lead.

Cadmium also affects the toxicity of lead. A synergistic effect of these metals was found on prostatic cytology and testicular damage in male rats following intraperitoneal injection (Fahim and Khare 1980). Rats fed lead and cadmium or zinc had a marked reduction of reticulocytosis compared with rats fed lead alone (Thawley et al. 1977). Mice exposed simultaneously to lead and cadmium for 10 weeks had higher

TABLE 2-8. Effects of Nutritional Factors on Lead Uptake in Animals

Factor	Species	Index of effect	Interactive effect	References
Calcium	Rat	Lead in tissues and severity of effect at low levels of dietary calcium	Low dietary calcium (0.1%) increase lead absorption and severity of effects	Six and Goyer 1970; Mahaffey et al. 1973
Calcium	Pig	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Hsu et al. 1975
Calcium	Horse	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Willoughby et al. 1972
Calcium	Lamb	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Morrison et al. 1977
Calcium	Rat	Lead retention	Retention increased in calcium deficiency	Barton et al. 1978a
Iron	Rat	Tissue levels and relative toxicity of lead	Iron deficiency increases lead absorption and toxicity	Six and Goyer 1972
Iron	Rat	Lead absorption in everted duodenal sac preparation	Reduction in intubated iron increases lead absorption; increased levels decrease lead uptake	Barton et al. 1978b
Iron	Mouse	Lead retention	Iron deficiency has no effect on lead retention	Hamilton 1978
Protein	Rat	Body lead retention	Low dietary protein either reduces or does not affect retention in various tissues	Quarterman et al. 1978
Protein	Rat	Tissue levels of lead	Casein diet increases lead uptake compared to soybean meal	Anders et al. 1982

TABLE 2-8 (Continued)

Factor	Species	Index of effect	Interactive effect	References
Milk components	Rat	Lead absorption	Lactose-hydrolyzed milk does not increase lead absorption, but ordinary milk does	Bell and Spickett 1981
Milk components	Rat	Lead absorption	Lactose in diet enhances lead absorption compared to glucose	Bushnell and DeLuca 1981
Zinc	Rat	Lead absorption	Low zinc in diets increases lead absorption	Cerklewski and Forbes 1976
Zinc	Rat	Lead transfer in utero and in milk during lactation	Low-zinc diet of mother increases lead transfer in utero and in maternal milk	Cerklewski 1979
Zinc	Rat	Tissue retention	Low zinc diet enhances brain lead levels	Bushnell and Levin 1983
Copper	Rat	Lead absorption	Low copper in diet increases lead absorption	Klauder and Petering 1975
Iron	Rat	In utero or milk transfer of lead in pregnant or lactating rats	Iron deficiency increases both in utero and milk transfer of lead to sucklings	Cerklewski 1980
Phosphorus	Rat	Lead uptake in tissues	Reduced phosphorus increases ^{203}Pb uptake 2.7-fold	Barltrop and Khoo 1975
Phosphorus	Rat	Lead retention	Low dietary phosphorus enhances lead retention; no effect on lead resorption in bone	Quarterman and Morrison 1975

TABLE 2-8 (Continued)

Factor	Species	Index of effect	Interactive effect	References
Phosphorus	Rat	Lead retention	Low dietary phosphorus enhances both lead retention and lead deposition in bone	Barton and Conrad 1981
Vitamin D	Rat	Lead absorption using everted sac techniques	Increasing vitamin D increases intubated lead absorption	Smith et al. 1978
Vitamin D	Rat	Lead absorption using everted sac techniques	Both low and excess levels of vitamin D increase lead uptake by affecting motility	Barton et al. 1980
Lipid	Rat	Lead absorption	Increases in lipid (corn oil) content up to 40% enhance lead absorption	Barltrop and Khoo 1975
Protein	Rat	Lead uptake by tissues	Both low and high protein in diet increases lead absorption	Barltrop and Khoo 1975

^{203}Pb = Lead 203

mortality rates than mice exposed to either metal alone (Exon et al. 1979). In addition, interactions between cadmium and lead have been reported at the behavioral level (Nation et al. 1990).

Several interactions of lead and iron have been documented in animals. Low dietary iron tends to increase the susceptibility to lead intoxication because of enhanced gastrointestinal absorption, suggesting a common absorption pathway for these two elements (Six and Goyer 1972). There is a synergistic action between lead intoxication and iron deficiency on impairment of hematopoiesis, specifically on hemoglobin level and red blood cell size (Hashmi et al. 1989a; Waxman and Rabinowitz 1966). In addition, iron and lead appear to be antagonistic with respect to ALAD activity; iron deficiency enhances blood ALAD activity while lead exposure suppresses ALAD activity (Hashmi et al. 1989a). Iron appeared to reduce the effects of orally or subcutaneously administered lead on blood enzyme and liver catalase activity (Bota et al. 1982). Treatment of pregnant hamsters with iron- or calcium-deficient diets in conjunction with orally administered lead resulted in embryonic or fetal mortality and abnormalities (runting, edema) in the litters, while treatment with complete diets and lead did not (Carpenter 1982). Inadequate levels of iron in association with increased body burdens of lead enhanced biochemical changes associated with lead intoxication (Waxman and Rabinowitz 1966). Ferrous iron was reported to protect against the inhibition of hemoglobin synthesis and cell metabolism by lead; it has been speculated that iron competes with lead uptake by the cell (Waxman and Rabinowitz 1966). In addition, the incorporation of iron into heme in the mouse embryonic liver was greatly decreased in lead-treated mice, resulting in retarded embryo growth due to impaired heme synthesis (Gerber and Maes 1978). Another study demonstrated that iron and lead were synergistic in reducing liver and kidney iron levels, but not copper levels (Hashmi et al. 1989b).

Dietary copper also appears to be antagonistic to the adverse effects of lead on the hematopoietic system, growth depression or tissue hypertrophy (Klauder and Petering 1975). The reduction in uptake of lead and decrease of lead-induced ALAD inhibition upon administration of copper may be achieved through a competition between the two metals for binding to proteins (Underwood 1977).

Zinc may have a protective effect against lead toxicity. Zinc added in the diet has been found to protect horses grazing on lead-contaminated pastures from clinical signs of lead toxicity (Goyer 1986). Zinc almost entirely eliminated the inhibition of ALAD by lead in rabbits (Haeger-Aronsen et al. 1976) and was shown to protect rats against the effects of orally administered lead (Brewer et al. 1985; Cerklewski and Forbes 1976), even during gestation and lactation (Cerklewski 1979). A protective effect of zinc against lead toxicity in the chick embryo has also been shown (Srivastava and Tandon 1984). In addition, lead exposure and zinc deficiency exerted additive effects on decreased body weights of rats (Bushnell and Levin 1983). The protective action of zinc on lead toxicity is thought to be mediated by an inhibition of gastrointestinal absorption via an intestinal metallothionein mechanism, which binds lead (Brewer et al. 1985; Cerklewski and Forbes 1976). Also, excess zinc protects zinc-containing enzymes like ALAS, ferrochelatase, and ALAD. In vivo, aqueous solution containing zinc administered to rats significantly reduced the genotoxic effects induced by lead (Kowalska-Wochna et al. 1988). It was postulated that zinc's protective action may be related to its functioning in DNA and RNA polymerases and consequent enhancement of cell repair processes.

Evidence suggests that lead exacerbates the toxic effects of mercury. In the rat, the administration of lead nitrate increased kidney and liver glutathione content and resulted in increased mercury deposition in the kidney, along with increased lethality in rats (Congiu et al. 1979).

The interaction of lead and ethanol has been studied by Flora and Tandon (1987), who suggested that rats exposed to lead and ethanol are more susceptible to the neurological and hepatotoxic effects of lead. In this study, the simultaneous exposure of rats to lead and ethanol resulted in a significantly higher concentration of lead in blood, brain, and liver tissues compared with rats treated with lead alone. Lead given with ethanol resulted in more pronounced inhibition of the activities of hepatic glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) than did treatment with lead by itself. In addition, exposure to lead plus ethanol resulted in a greater depression of dopamine and 5-hydroxytryptamine levels in the rat brain than did lead treatment alone. A subsequent study conducted by the same investigators, found that rats co-exposed to lead and ethanol (20% in drinking water) experienced more marked inhibition of blood ALAD activity, elevation of blood ZPP, urinary elimination of lead and ALA, and increased blood, liver, kidney, and brain lead levels than rats exposed to lead alone (Dhawan et al. 1989).

Another study investigated the interactive effects of lead and alcohol during pregnancy on the fetal development and offspring learning (Zajac and Abel 1990). No differences were found in maternal weight gain, percent resorptions, litter size or fetal weight in rats treated simultaneously with lead and alcohol, compared with alcohol-treated rats; however, these parameters were significantly different for lead-plus-alcohol-dosed rats compared with lead-treated rats. In addition, no potentiation of activity, passive avoidance, or active avoidance learning was observed compared to animals treated with alcohol or lead alone. The authors concluded that neither lead nor alcohol attenuate or potentiate each other's effects on reproduction or learning behavior.

Gelman et al. (1978) found that the interaction between lead and phenylhydrazine produced an additive effect in the acute hemolytic phase of anemia and a probable synergistic effect during the compensatory phase of anemia in rabbits. The mechanism postulated for anemic interaction appears to be primarily related to depressed bone marrow production of erythrocytes rather than to increased hemolysis.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population exhibits different or enhanced response to lead than do most persons exposed to the same level of lead in the environment. Reasons include genetic make-up, developmental stage, health and nutritional status, and chemical exposure history. These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic and renal) or the pre-existing compromised function of target organs. For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs generally to be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, "Populations With Potentially High Exposure."

Certain subgroups of the population may be more susceptible to the toxic effects of lead exposure. These include preschool age children (<6 years old), pregnant women, the elderly, smokers, alcoholics, and people with genetic diseases affecting heme synthesis, nutritional deficiencies, and neurological or kidney dysfunction.

Children are at the greatest risk for experiencing lead-induced health effects, particularly in the urbanized, low-income segments of this pediatric population. Young children (<5 years old) have been documented to absorb lead via the gastrointestinal tract more efficiently (50% relative absorption) than adults (15% relative absorption) (Chamberlain et al. 1978). The use of leaded seams in cans used for canned food is not nearly as prevalent as it once was, so this is no longer as important a source of dietary exposure exposure to lead. Behavior such as thumb sucking and pica result in an elevated transfer of lead-contaminated dust and dirt to the gastrointestinal tract (Schroeder and Hawk 1987). Children also have immature detoxification enzyme systems, resulting in increased retention and body burdens of lead and frequently have a greater prevalence of nutrient deficiency (Yip et al. 1981; Ziegler et al. 1978). For example, the diets of young children are commonly deficient in zinc, a condition that exacerbates some of the toxic effects of lead. Children have also been documented to have lower blood thresholds for the hematological and neurological effects induced by lead exposure. In addition, the resultant encephalopathy, central nervous system deficits, and neurologic sequelae tend to be much more severe in children than adults (Bellinger et al. 1988; Bradley et al. 1956; Wang et al. 1989).

Susceptibility to lead toxicity is influenced by dietary levels of calcium, iron, phosphorus, vitamins A and D, dietary protein, and alcohol (Calabrese 1978). Low dietary ingestion of calcium or iron increased the predisposition to lead toxicity in animals (Barton et al. 1978a; Carpenter 1982; Hashmi et al. 1989a; Six and Goyer 1972; Waxman and Rabinowitz 1966). Iron deficiency combined with lead exposure acts synergistically to impair heme synthesis and cell metabolism (Waxman and Rabinowitz 1966). Nutritional surveys indicate that children of low-income groups consume less than recommended dietary allowances of calcium and iron. Dietary deficiencies of these two minerals have been shown to potentiate the toxicity of lead (Johnson and Tenuta 1979; Yip et al. 1981; Ziegler et al. 1978). Thus, nutrient deficiencies in conjunction with a developmental predisposition to absorb lead makes this subset of children at a substantially elevated risk.

Pregnant women are at increased risk because of the inherent susceptibility of the fetus, arising from transplacental transfer of maternal lead (Bellinger et al. 1987a; Moore et al. 1982). Lead has been demonstrated in animal studies to increase the incidence of fetal resorptions (McClain and Becker 1972) and to induce adverse neurobehavioral effects in offspring exposed in utero (Draski et al. 1989).

Recent data suggest that conditions of pregnancy, lactation, and osteoporosis may intensify bone demineralization, thus mobilizing bone lead into the blood resulting in increased body burdens of lead (Silbergeld et al. 1988). For example, women show an increased rate of bone lead loss with age relative to men (Drasch et al. 1987). Women with postmenopausal osteoporosis may be at an increased risk since lead inhibits activation of vitamin D, uptake of calcium, and several aspects of bone cell function to aggravate the course of osteoporosis. Using data collected from 2,981 women in the NHANES II study, a significant increase in blood lead levels was observed after menopause (Silbergeld et al. 1988). However, the actual prevalence of osteoporosis was not reported in this study, so it is not possible to conclude that increased mobilization of lead from bone in postmenopausal women is directly related to an increased incidence of osteoporosis based on these data. Furthermore, in a study of 3,098 55–66-year-old women, it was found that blood lead levels were not elevated to toxic levels as a result of lead mobilization from bone during conditions of bone demineralization, such as osteoporosis (Ewers et al. 1990). The highest blood lead levels measured in this study ranged from 15 to 30 μg/dL. Lead mobilization also has toxic implications for both the unborn and newborn who may be exposed to elevated concentrations of lead in utero and during nursing.

The aged population may be at an increased risk for toxic effects of lead. In addition to the mobilization of bone lead and increased lead body burden due to osteoporosis, recent animal data suggest that aged animals may be more susceptible to the effects of lead than adult or young animals (Cory-Slechta 1990b). For example, increases in ZPP and urinary ALA were observed in aged rats sooner than in young or adult rats with comparable blood lead levels. Also, aged rats exposed to lead had a higher mortality rate than nonexposed aged rats.

The toxic effects of lead exposure become exacerbated in individuals with inherited genetic diseases, such as thalassemia, which is characterized by an abnormality in the rate of hemoglobin synthesis (Calabrese 1978). Individuals with glucose-6-phosphate dehydrogenase deficiency are also unusually susceptible and may exhibit hemolytic anemia following lead exposure (Calabrese 1978). It has also been postulated that children with sickle cell disease have an increased risk of developing neuropathy with exposure to lead (Erenberg et al. 1974). People with metabolic disorders associated with the synthesis of porphyrins (important intermediates in the synthesis of hemoglobin, cytochromes, and vitamin B_{12}), collectively known as porphyrias, are especially susceptible to lead exposure since lead inhibits two critical enzymes, ALAD and ferrochelatase, concerned with heme synthesis in erythrocytes (Hubermont et al. 1976; Silbergeld et al. 1982). The presence of genetic disorders that induce excessive ALA synthetase activity in addition to lead exposure produce higher than normal levels of ALA, resulting in excessive ALA excretion, accumulation, and lack of negative feedback on the ALA synthetase activity from heme (Calabrese 1978).

Alcoholics, and people who consume excess amounts of alcohol, may be at increased risk of hematological, neurological, and hepatotoxic effects. In animal studies, lead and alcohol synergistically inhibited blood ALAD activity and hepatic glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) activity, depressed dopamine and 5-hydroxytryptamine levels in rat brain, increased lead burdens in tissue organs, and elevated blood ZPP (Dhawan et al. 1989; Flora and Tandon 1987). Smokers are also at elevated risks of lead intoxication since cigarette smoke contains lead and other heavy metals such as cadmium and mercury (Calabrese 1978), which have been shown to be synergistic in experimental animals (Congiu et al. 1979; Exon et al. 1979; Fahim and Khare 1980).

People with neurologic dysfunction or kidney disease are unusually susceptible to lead exposure. These are the primary target organs of lead intoxication, which may become overburdened at much lower threshold concentrations to elicit manifestations of lead intoxication (Benetou-Marantidou et al. 1988; Chisolm 1962, 1968; Lilis et al. 1968; Pollock and Ibels 1986).

2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to lead. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to lead. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.8.1 Reducing Peak Absorption Following Exposure

Individuals potentially exposed to lead can prevent inhalation exposure to particles by wearing the appropriate respirator. The mechanism and rate of lead absorption from the gastrointestinal tract is not completely understood, but it is believed that absorption occurs in the small intestine by both active and passive transport following solubilization of lead salts by gastric acid (Ellenhorn and Barceloux 1988; Haddad and Winchester 1990). Lead is poorly absorbed from the gastrointestinal tract; however, toxic effects can result from the relatively small amount of lead that is absorbed. It has been estimated that approximately 10% of an administered dose is absorbed by adults and 4–50% of ingested lead is absorbed by children (Chamberlain et al. 1978). Lead absorption from the gut appears to be blocked by calcium, iron, and zinc (Haddad and Winchester 1990). Although no treatment modalities to reduce lead absorption have yet been developed that make use of these observations; it is recommended that a child's diet contain ample amounts of iron and calcium to reduce the likelihood of increased absorption of lead (CDC 1991). General recommendations to reduce absorption following acute exposure to lead, include removing the individual from the source of exposure and decontaminating exposed areas of the body. Contaminated skin is washed with soap and water, and eyes exposed to lead are thoroughly flushed with water or saline (Stutz and Janusz 1988). Once lead is ingested, it is suggested that syrup of ipecac be administered to induce emesis. Administration of activated charcoal following emesis has not been proven to reduce absorption of any lead remaining in the gastrointestinal system, but is frequently recommended (Stutz and Janusz 1988). Gastric lavage has been used to remove ingested lead compounds. Whole gut lavage with an osmotically neutral (polyethylene glycol electrolyte solution [GO-Lytely®, Co-lyte®) has successfully removed ingested lead-containing pottery glazes in anecdotal case reports. However, this procedure is not universally accepted. Patients who ingest lead foreign objects should be observed for the possible, although rare, development of signs or symptoms of lead poisoning until the ingested object has been proven to have passed through the gut. Surgical excision is recommended when lead bullets or shrapnel are lodged near joint capsules (reaction with synovial fluid leads to systemic uptake of lead in some cases). The blood lead level can be monitored and used as an indication for surgical removal of the projectile.

2.8.2 Reducing Body Burden

Lead is initially distributed throughout the body and then redistributed to soft tissues and bone. In human adults and children, approximately 94% and 73% of the total body burden of lead is found in bones, respectively. Lead may be stored in bone for long periods of time, but may be mobilized thus achieving a steady state of intercompartmental distribution (see Section 2.3.2).

All of the currently available methods to obviate the toxic effects of lead are based on their ability to reduce the body burden of lead by chelation. All of the chelating agents bind inorganic lead, enhance its excretion, and facilitate the transfer of lead from soft tissues to the circulation where it can be excreted. Since the success of chelation therapy depends on excretion of chelated lead via the kidney, caution should be used when treating a patient with renal failure. The standard chelating agents currently in use are dimercaprol (British Anti-Lewisite, or BAL) and $CaNa_2$-EDTA (or EDTA). Both of these agents are administered parenterally. Penicillamine has been used as an oral chelating agent. It increases urinary excretion of lead by an unknown mechanism but is not as effective as EDTA and is not yet approved for use by the FDA for lead poisoning (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; Haddad and Winchester 1990). The preferred chelating agent and the treatment regimen depend on the nature of the intoxication (i.e., the symptomology present and the extent of lead exposure as determined by blood lead level). BAL chelates both intracellular and extracellular stores. BAL-lead chelates are excreted primarily in the bile, with some excretion in the urine. Thus, in individuals with kidney impairment, BAL is the chelating agent of choice. EDTA mobilizes lead from bone and soft tissue stores, and thus may aggravate acute toxic symptoms by increasing blood lead if not given in conjunction with BAL. Therefore, for adults that are symptomatic or have blood lead levels >70 μg/dL and for children (symptomatic or asymptomatic) with blood lead levels >70 μg/dL, therapy with BAL followed by EDTA is used (CDC 1991; Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; Haddad and Winchester 1990). For asymptomatic children with blood lead levels of 45–69 μg/dL, a course of EDTA chelation therapy is used (CDC 1991; Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; Haddad and Winchester 1990). 2,3-Dimercaptoseccinia acid (DSMA; Succimer®) is an orally administered chelating agent recently approved by the FDA for treating children with blood lead levels >45 mg/dL, for which indication it is the treatment of choice. Although not yet FDA labelled for this indication, DSMA is also being used to treat lead poisoning in adults. The effectiveness of chelation therapy for treating children with blood lead levels ranging from 25 to 44 μg/dL has not been demonstrated, and treatment of children in this range varies. Some practitioners employ chelation therapy for the treatment of children with blood lead levels of 25–44 μg/dL. At a minimum, it is recommended that exposure to lead be minimized, sufficient calcium and iron intake be ensured, and regular blood lead level testing be conducted in children who fall into this range (CDC 1991). Children with blood lead levels of 20–24 μg/dL are generally not chelated. Management of these children includes reducing sources of lead exposure, ensuring proper nutritional status, and routine blood lead testing (CDC 1991).

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

The diffuse effects of lead are thought to be the result of its ability to combine with ligand groups (predominantly sulfhydryl groups) on proteins, thereby affecting many enzyme systems and cellular processes throughout the body (e.g., the enzymes involved in heme synthesis, see Sections 2.2.1.2 and 2.4) (Ellenhorn and Barceloux 1988; Haddad and Winchester 1990). Therefore, interfering with the binding of lead to these macromolecules would reduce the toxicity of lead. For example, the efficacy of treatment with a sulfhydryl donor for lead to bind to, such as acetylcysteine, could be investigated. The chelating agents discussed in Section 2.8.2 bind to lead and, therefore, prevent its binding to proteins. All chelating agents have more or less significant potential adverse effects, and some are contraindicated or must be used with extreme caution in some situations or in some patients (e.g., patients with renal impairment). It is advisable to consult with a medical toxicologist or other physician familiar with those medications before commencing treatment.

In cases of lead encephalopathy with cerebral edema, edema can be treated with mannitol, corticosteroids, and hypothermia. Convulsions can be treated with diazepam, phenytoin, and/or phenobarbital (Garrettson 1990).

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of lead is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of lead.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of Lead

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to lead are summarized in Figure 2-9. The purpose of this figure is to illustrate the existing information concerning the health effects of lead. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information (i.e., data gaps that must necessarily be filled).

2.9.2 Identification of Data Needs

Acute-Duration Exposure. There are few data available for acute exposures in humans. This may be a function of the time required for the expression of effects (decreased heme synthesis, neurobehavioral changes, increased blood pressure, and interference with vitamin D metabolism) and the usual modes of exposure in humans, which are repeated ingestion of lead-containing dirt or paint chips in children and continuous occupational inhalation exposures for adults. One case report reviewed described a patient that presented with headache, fatigue, nausea, abdominal cramps, and arthralgias with a blood lead level of 90 μg/dL following a 12-hour exposure to lead from sandblasting old lead-based paint, indicating that lead toxicity can occur in humans after acute-duration exposures (Schneitzer et al. 1990). Some data exist that show death occurred in children who had severe lead-induced encephalopathy (Chisolm 1962; Chisolm and Harrison 1956). The duration of exposure associated with this effect is not clear; it may have been a few weeks or more and, in some cases, may have been acute. There are data that show human ingestion of lead acetate produced a decrease in erythrocyte ALAD within 3 days (Stuik 1974). There are no data available on acute inhalation exposures in animals.

A 7-day oral study in rats fed lead acetate (Smith et al. 1981) reported a depression of 1,25-dihydroxyvitamin D plasma levels providing support for the evidence seen in humans that vitamin D metabolism may be a target for lead toxicity. No acute MRLs have been determined because no thresholds have been demonstrated for the most sensitive effects in humans--heme synthesis, erythropoiesis, neurobehavioral toxicity, and cardiovascular toxicity. Additional data relating environmental measurements of exposure, blood lead levels, and toxic effects from acute inhalation and oral exposures would be useful for assessment of the public health concern with acute exposure to lead. Further data that provided dose-response information would be useful for determining if there is a threshold for lead toxicity in animals and, if so, the thresholds for lead toxicity for both oral and inhalation exposures. There are no pharmacokinetic data that specifically address whether or not the route of exposure alters the health effects caused by lead, but the available information indicates that the toxic effects of lead are the same regardless of route of exposure. Dermal exposures are not considered to be significant in humans because the dermal absorption rate of lead is so low for inorganic compounds. Significant dermal exposure occurs for organolead compounds.

Intermediate-Duration Exposure. Intermediate and chronic exposures in humans should be considered together, because the length of exposure is not usually known. The database for lead is unusual in that it contains a great deal of data concerning dose-effect relationships in humans. However, the dose data for humans are usually expressed in terms of blood lead levels rather than as environmental exposure levels. Dose-effect data in terms of environmental levels (mg/kg/day or mg/m^3) by a single route of exposure are not generally available for humans.

The dose-effect relationship between blood lead and ALAD has been reported to extend through the lowest blood lead levels detectable (Chisolm et al. 1985; Hernberg and Nikkanen 1970; Lauwerys et al. 1978; Roels and Lauwerys 1987; Secchi et al. 1974). Inhibition of enzyme activity results in reduced heme synthesis, which affects not only the oxygen-carrying potential of erythrocytes but also decreases formation of cytochrome P-450. This effect can influence many metabolic energy-transfer processes. Formation of heme-containing cytochromes is also inhibited in animals treated intraperitoneally or orally with lead compounds (Azar et al. 1973; Goldbert et al. 1978; Krasovskii et al. 1979; Overmann 1977; Walsh and Ryden 1984). No intermediate MRLs have been determined because no thresholds have been demonstrated for the most sensitive effects in humans--heme synthesis, erythropoiesis, and neurobehavioral toxicity. Additional data from 90-day animal studies would be useful for correlating environmental exposure

FIGURE 2-9. Existing Information on Health Effects of Lead

	Death	Systemic: Acute	Systemic: Intermed.	Systemic: Chronic	Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
Inhalation	●	●	●	●	●	●	●	●	●	●
Oral	●	●	●	●	●	●	●	●	●	●
Dermal										

HUMAN

	Death	Systemic: Acute	Systemic: Intermed.	Systemic: Chronic	Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
Inhalation			●		●		●			
Oral	●	●	●	●	●	●	●	●	●	●
Dermal										●

ANIMAL

● Existing Studies

measurements with both blood lead levels and health effects. Further data that provided dose-response information would be useful for determining if there is a threshold for lead toxicity and, if so, the thresholds for lead toxicity for both oral and inhalation exposures. There are no pharmacokinetic data that specifically address whether or not the route of exposure alters the health effects caused by lead, but the available information indicates that the toxic effects of lead are the same regardless of route of exposure. Dermal exposures are not considered to be significant in humans because the dermal absorption rate of inorganic lead is so low. Organic lead compounds can be significantly absorbed following dermal exposure.

Chronic-Duration Exposure and Cancer. As stated in the preceding section, intermediate and chronic exposures in humans should be considered together, because the length of exposure is usually not known. Effects on heme synthesis and erythropoiesis (Adebonojo 1974; Alessio et al. 1976; Awad et al. 1986; Baker et al. 1979; Betts et al. 1973; Chisolm et al. 1985; Grandjean 1979; Hernberg and Nikkanen 1970; Lauwerys et al. 1974, 1978; Lilis et al. 1978; Meredith et al. 1978; Pollock and Ibels 1986; Roels and Lauwerys 1987; Roels et al. 1975, 1976, 1979; Rosen et al. 1974; Schwartz et al. 1990; Secchi et al. 1974; Selander and Cramer 1970), neurobehavioral toxicity (Arnvig et al. 1980; Awad et al. 1986; Baker et al. 1979; Baloh et al. 1979; Campara et al. 1984; de la Burde and Choate 1972, 1975; Ernhart et al. 1981; Glickman et al. 1984; Haenninen et al. 1979; Hogstedt et al. 1983; Holness and Nethercott 1988; Khera et al. 1980b; Kotok 1972; Kotok et al. 1977; Mantere et al. 1982; Marino et al. 1989; Matte et al. 1989; Pagluica et al. 1990; Parkinson et al. 1986; Pasternak et al. 1989; Pollock and Ibels 1986; Rummo et al. 1979; Schneitzer et al. 1990; Zimmerman-Tansella et al. 1983), cardiovascular toxicity (de Kort et al. 1987; Kirkby and Gyntelberg 1985; Kline 1960; Kosmider and Petelenz 1962; Pocock et al. 1984, 1985, 1988; Pollock and Ibels 1986; Marino et al. 1989; Silver and Rodriquez-Torres 1968; Weiss et al. 1986, 1988), renal toxicity (Batuman et al. 1981, 1983; Biagini et al. 1977; Chisolm 1962; Cramer et al. 1974; Lilis et al. 1968; Maranelli and Apostoli 1987; Ong et al. 1987; Pollock and Ibels 1986; Pueschel et al. 1972; Verschoor et al. 1987; Wedeen et al. 1979), and vitamin D metabolism (Mahaffey et al. 1982; Rosen et al. 1980) have been noted. No chronic MRLs have been determined because no thresholds have been demonstrated for the most sensitive effects in humans--heme synthesis, erythropoiesis, and neurobehavioral toxicity. Additional data providing dose-response information would be useful for determining if there is a threshold for lead toxicity and, if so, the thresholds for lead toxicity for both oral and inhalation exposures. There are no pharmacokinetic data that specifically address whether or not the route of exposure alters the health effects caused by lead, but the available information indicates that the toxic effects of lead are the same regardless of route of exposure. Dermal exposures are not considered to be significant in humans because the dermal absorption rate of lead is so low.

Several epidemiological studies of occupationally exposed persons have examined the potential carcinogenicity of lead (Cooper 1976; Cooper and Gaffey 1975; Fayerweather et al. 1991; Kang et al. 1980; Selevan et al. 1985). These studies all exhibit some methodological limitations, which include no identification of the actual lead compounds to which exposure occurred, no specification of the route of exposure, no adjustment for concomitant exposure to other chemicals and no adjustment for other confounders, such as cigarette smoking. Increased incidences of total malignant neoplasms were reported in some studies; statistical significance was reached in some categories, but not others. One study reported a non-significant increase in renal cancer, which is supportive of animal studies that associate lead exposure with kidney cancer (Selevan et al. 1985). Two additional case reports of renal cancer in occupationally exposed men also provide anecdotal support for this evidence (Baker et al. 1980; Lilis 1981). These case reports are the only occupational cancer reports to include blood lead levels. There are no data regarding the carcinogenicity of lead in humans exposed solely by the oral route.

Several animal studies associate oral exposure to several lead compounds with renal tumors in various species (Azar et al. 1973; Koller et al. 1985; Van Esch and Kroes 1969). Most studies used one or two doses; good dose-effect data are not available. One 2-year study in rats used six doses as well as a control group (Azar et al. 1973). This study measured both exposure levels and blood levels, and correlated these with increased tumor incidence, as well as reduced heme synthesis. There are no animal data on the carcinogenicity of lead by inhalation exposure. Additional long-term studies of other species would be valuable for providing insight into the equivocal findings of carcinogenesis in humans. Information on inhalation exposures would be particularly useful because most long-term human exposures are thought to be occupational and primarily inhalation. There are recognized species differences in the pharmacokinetics of lead that may have a bearing on the carcinogenic potential for this compound across species (see "Comparative Toxicokinetics").

Genotoxicity. There are data on the genotoxicity of lead both from in vitro and in vivo studies. Human lymphocytes have been examined from both occupationally or environmentally exposed persons and from healthy controls as well (Beek and Obe 1974; Deknudt and Deminatti 1978; Gasiorek and Bauchinger 1981; Niebuhr and Wulf 1984; Schmid et al. 1972). The results of these studies are mixed. The positive data indicate that lead is a clastogen. The results of in vivo tests are also contradictory, but do suggest that lead has an effect on chromosomes. Increased sister chromatid exchange was seen in one study of lead-exposed workers (Huang et al. 1988b), but this was not seen in another study (Maki-Paakkanen et al. 1981). There was a positive correlation in one study of increased frequency of sister chromatid exchange and of duration of occupational exposure independent of blood level (Grandjean et al. 1983). A positive correlation between chromosomal aberrations and blood levels has been reported (Huang et al. 1988b). In mammalian test systems in vitro, lead acetate gave conflicting results for structural chromosomal aberrations (Bauchinger and Schmid 1972; Robison et al. 1984).

Tests for gene mutations, DNA modifications, and recombinations in various microorganisms using lead acetate, lead nitrate, and lead chloride were consistently negative with or without metabolic activation (Bruce and Heddle 1979; Dunkel et al. 1984; Fukunaga et al. 1982; Hoffman and Niyogi 1977; Kharab and Singh 1985; Nestmann et al. 1979; Nishioka 1975; Rosenkranz and Poirier 1979; Simmon 1979a, 1979b; Sirover and Loeb 1976). There are some data to indicate that the status of calcium availability may be important in the expression of lead-induced clastogenicity in both in vitro and in vivo tests (Deknudt et al. 1977; Hartwig et al. 1990). Studies in monkeys indicated that calcium deficiency may enhance the genotoxicity of lead as it does other manifestations of lead toxicity (Deknudt et al. 1977). Further studies to clarify the clastogenic potential of lead and its compounds would be useful in assessing possible implications for carcinogenic potential. Specific aberrations, if identified, could offer insight into a mechanism for carcinogenesis.

Reproductive Toxicity. Human data on reproductive toxicity come from observations in occupational cohorts (Assennato et al. 1987; Baghurst et al. 1987; Braunstein et al. 1978; Chowdhury et al. 1986; Cullen et al. 1984; Hu et al. 1991; Lancranjan et al. 1975; McMichael et al. 1986; Murphy et al. 1990; Nordstrom et al. 1979; Rodamilans et al. 1988; Wibberley et al. 1977; Wildt et al. 1983). Although no dose-effect data were presented, occupational exposure to inorganic lead has been associated with a high likelihood of spontaneous abortion (Baghurst et al. 1987; Hu et al. 1991; McMichael et al. 1986; Nordstrom et al. 1979; Wibberley et al. 1977). Studies of increased frequency of spontaneous abortion in women living closest to a lead smelter or working in highly contaminated areas of the smelter were confounded by the presence of other toxic agents and by the lack of matching for socioeconomic status. There are data that indicate that reproductive effects occur in men exposed to lead manifested as asthenospermia, hypospermia, and teratospermia, and that these effects are related to blood lead levels (Assennato et al. 1987; Braunstein et al. 1978; Chowdhury et al. 1986; Cullen et al. 1984; Lancranjan et al. 1975; Rodamilans et al. 1988; Wildt et al. 1983).

Animal studies support the evidence of lead-induced reproductive toxicity in humans. Rats dosed with oral lead acetate show irregular estrous cycles in females and testicular damage in males (Hilderbrand et al. 1973). There are no data on the reproductive toxicity of inhaled lead in animals.

There are enough well-reported data to provide qualitative evidence in support of the association with high levels of lead and reproductive effects in humans and animals. However, the data cannot be used to estimate effect levels in women and can be used only with caution to describe effects on sperm or testes from specific blood levels of lead. Additional dose-effect data on inhalation exposures in humans would be useful for determining extent of exposure required to produce reproductive effects, as inhalation exposures are the most common in occupationally exposed adults. Ninety-day inhalation animal studies with lead that examined the reproductive organ pathology would be useful for confirming the qualitative data available for humans.

Developmental Toxicity. Three recent human studies that described congenital malformations as an end point allow no definitive conclusion to be drawn regarding an association between prenatal lead exposure and the occurrence of congenital anomalies (Ernhart et al. 1985, 1986; McMichael et al. 1986; Needleman et al. 1984). The limitations of these studies include possible bias introduced by use of hospital records and a restricted range of maternal and cord blood lead levels. The sizes of the groups studied were not sufficient for the detection of differences in low frequencies of anomalies.

The data are mixed regarding reduced birth weight and prenatal lead exposure in humans. Studies evaluating exposure to low levels of lead and its influence upon birth weight and gestational age are more controversial. The earlier evidence for such effects has not been reproduced in the more recent studies by Factor-Litvak et al. (1991) and Greene and Ernhart (1991). A significant inverse association between prenatal maternal blood lead levels and birth weight was reported in the Cincinnati study (Bornschein et al. 1989; Dietrich et al. 1986, 1987a). An earlier study showed that the percentage of small-for-gestational-age infants increased with increasing cord blood lead, although the trend was not quite statistically significant (Bellinger et al. 1984). Significant direct associations between maternal and cord blood lead levels and birth weight were reported by McMichael et al. (1986). On the other hand, no association has been observed between maternal or cord blood levels and birth weight in several other studies (Ernhart et al. 1985, 1986; Factor-Litvak et al. 1991; Greene and Ernhart 1991; Moore et al. 1982; Needleman et al. 1984;).

Evidence from some of the above studies also indicates that gestational age may be reduced as prenatal lead exposure increases, even at blood lead levels below 15 μg/dL (EPA 1986a). Significant negative correlations between maternal or cord blood lead levels and gestational age were reported by Dietrich et al. (1986, 1987), McMichael et al. (1986); and Moore et al. (1982). Based on parameter estimates of Dietrich et al. (1986), the reduction in gestational age was 0.6 week per natural log unit of blood lead increase (EPA 1986a). Based on risk estimates of McMichael et al. (1986), the risk of preterm delivery increases by at least fourfold as either cord blood or maternal blood lead level at delivery increases from ≤ 8 to >14 μg/dL. However, other investigators did not find a significant relationship between maternal or cord blood lead level and gestational age (Bellinger et al. 1984; Factor-Litvak et al. 1991; Needleman et al. 1984). These studies also indicate that adverse neurobehavioral affects can occur because of prenatal lead exposure (see the discussion on "Neurotoxicity" below). Additional data on developmental effects would be useful for clarifying the inconsistencies seen in available study results. As most adult exposures associated with hazardous waste sites are via the inhalation or oral routes, studies examining these routes of exposure would be particularly useful.

Inhalation and oral teratogenicity studies in rats and mice provide no evidence that lead acetate or lead nitrate are teratogenic after oral or inhalation exposure (Draski et al. 1989; Grant et al. 1980; Kimmel et al. 1980; Miller et al. 1982; Prigge and Greve 1977; Rabe et al. 1985). Intravenous and intraperitoneal injection of lead acetate, chloride, or nitrate into pregnant rats, mice, or hamsters have produced malformations in several studies (Gale 1978; McClain and Becker 1972; Snowden 1973). Based on these results, it would appear that parenteral administration of lead leads to greater target tissue doses than oral or inhalation exposure. Additional data on dose-effect relationships for these exposure routes would be useful because these data, along with pharmacokinetic data, could be used to assess the apparent difference in blood lead effects if the compounds are injected versus a more conventional route of exposure, i.e., inhalation or oral.

Immunotoxicity. The data in humans are limited to a few studies of immune function in lead workers (inhalation exposure). One study reported significant suppression of IgA levels (Ewers et al. 1982). Another study indicated that serum immunoglobulin levels were not significantly altered (Alomran and Shleamoon 1988). Another large study examined several parameters of immune function (serum immunoglobulins, PHA response, and natural killer cell activity) and found no differences in exposed workers and controls (Kimber et al. 1986b). The information available in children show no difference in several measures of immune response between children with blood lead ≥40 μg/dL and children without elevated blood lead (Reigart and Graber 1976).

The best human data available on immune response involve small numbers of subjects and lack of adequate controls. Further studies on immune function parameters in both children and adults would be useful for verifying or refuting the lack of immunotoxicity seen in humans to date.

One inhalation study in animals showed no effect on phagocytosis of bacteria in mice (Hillam and Ozkan 1986). No blood lead data were available. However, another intermediate-duration study in mice indicated that several components of the immune system were depressed following both inhalation and oral exposure, and that the immunosuppressive effect is most pronounced when the antigen is introduced by the same route as the pollutant (Hillam and Ozkan 1986). Dose-effect data for immune system effects at low blood levels and external lead exposure levels are available from rat studies (Faith et al. 1979; Giurgea et al. 1989; Kimber et al. 1986a; Luster et al. 1978;. Prenatal and postnatal exposure of rats to lead acetate at 25 ppm in drinking water resulted in marked depression of antibody responses to sheep red blood cells, decreased serum IgG, decreased lymphocyte responsiveness to mitogens, impaired delayed hypersensitivity reactions, and decreased thymus weights as compared with controls (Faith et al. 1979; Luster et al. 1978). Additional data from 90-day inhalation studies that would provide good dose-effect information on a variety of immune system parameters would be useful because the one study in mice suggest that lead-induced immunosuppression may be greater following inhalation exposure, and inhalation exposures can be significant for human adults. The available rat data are both quantitative and broad in scope. These positive data are suggestive of an effect on the immune system that may or may not be species specific. More information from other species would be useful to determine if immune effects are a common end point for lead toxicity.

Neurotoxicity. There is a very large database on the neurotoxic effects of lead. The most severe neurobehavioral effect of lead toxicity in adults is lead encephalopathy (Kehoe et al. 1961a; Kumar et al. 1987; Smith et al. 1978). Early symptoms, which may develop within weeks of initial exposure, include dullness, irritability, poor attention span, headache, muscular tremor, loss of memory, and hallucinations. These symptoms worsen, sometimes abruptly, to delirium, convulsions, paralysis, coma, and death. Other nervous system effects seen in adults at lower exposure levels include extensor muscle weakness, loss of appetite, paresthesias in lower limbs, weakness of upper limbs, poor performance on cognitive and visual-motor coordination tasks, and impaired verbal reasoning ability (Arnvig et al. 1980; Awad et al. 1986; Baker et al. 1979; Baloh et al. 1979; Campara et al. 1984; Glickman et al. 1984; Haenninen et al. 1979; Hogstedt et al. 1983; Holness and Nethercott 1988; Khera et al. 1980b; Mantere et al. 1982; Marino et al. 1989; Matte et al. 1989; Pagluica et al. 1990; Parkinson et al. 1986; Pasternak et al. 1989; Pollock and Ibels 1986; Schneitzer et al. 1990; Zimmerman-Tansella et al. 1983). Taken together, the results of these studies on adults (primarily occupational and therefore predominantly inhalation exposures) indicate that the blood lead levels at which neurological signs occur in adults is in the range of 40–60 μg/dL and that neurological effects occur at roughly the same blood lead levels as other symptoms of lead poisoning, such as gastrointestinal complaints.

In children, most exposures are oral, but the neurotoxic effects are similar to those seen in adults (Bradley and Baumgartner 1958; Bradley et al. 1956; Chisolm 1962, 1965; Chisolm and Harrison 1956; de la Burde and Choate 1972, 1975; Ernhart et al. 1981; Gant 1938; Kotok 1972; Kotok et al. 1977; Rummo et al. 1979; Smith et al. 1983). There are data available that indicate children with symptomatic lead poisoning without encephalopathy have an increased incidence of lasting neurological and behavioral impairments. While no adverse neurological effects have been clearly documented at low blood lead levels, decreased IQ associated with increased blood lead levels (>30 μg/dL) is well documented and some studies indicate that blood lead levels as low as 7 μg/dL may also decrease IQ (Bellinger and Needleman 1983; Bergomi et al. 1989; Fulton et al. 1987; Hansen et al. 1989; Hawk et al 1986; Needleman et al. 1979, 1985, 1990; Schroeder and Hawk 1987; Schroeder et al. 1985). These data suggest that children are more sensitive to lead-induced neurotoxicity than adults, as indicated by responses at lower blood levels. Pharmacokinetic data indicate that young children are more susceptible to the effects of lead because of the greater absorption and retention rates in children, a greater prevalence of nutrient deficiency, which can affect gastrointestinal absorption, differences in the efficiency of lead sequestration in bone, and incomplete development of the blood-brain barrier (Barry 1975; Chamberlain et al. 1978). Virtually all neurotoxic effects are reported as related to blood lead level. More information on the relationship of health effects to environmental exposure levels would be useful for quantifying the potential risk to environmentally exposed human populations. Additional data on the relationships between blood lead levels and environmental levels would also be useful for quantifying these risks and identifying threshold blood lead levels. In addition, further information on the pharmacokinetic differences in human adults and children would provide better data for risk estimation in susceptible groups.

There are no animal inhalation studies but many oral ones that describe adverse neurological effects (Bushnell and Bowman 1979a, 1979b; Bushnell and Levin 1983; Cory-Slechta et al. 1983, 1985; Ferguson and Bowman 1990; Gilbert and Rice 1987; Hopper et al. 1986; Krasovskii et al. 1979; Levin et al. 1988; Massaro and Massaro 1987; Overmann 1977; Rice 1985a). It appears that animals are affected at roughly the same blood lead levels as humans. Measured neurotoxic effects in animals include significantly delayed motor function and reflexes, decreased performance on learning tasks, and impaired spatial discrimination. Additional animal studies that investigated the neurotoxic effects of subchronic inhalation exposures would be useful for establishing external dose-effect relationships.

Epidemiological and Human Dosimetry Studies. There are dozens of epidemiological studies in both adults and children that investigate the health effects of lead. The general population is exposed to lead in ambient air, in many foods, in drinking water, and in dust. Segments of the general population at highest risk from lead exposure are preschool-age children (especially those in lower-income, inner city housing where there is old lead-based paint), pregnant women and their fetuses, and white males between 40 and 59 years of age. Within these groups, strong relationships have been established between lead exposure (as measured by blood lead levels) and adverse health effects. It is possible to measure lead in blood and bone, and there is a substantial body of data relating health effects to blood lead levels. The most obvious lack in the epidemiological studies is the absence of environmental measures of exposure. This kind of information would be useful for evaluating potential health effects for populations located near hazardous waste sites where potential exposure levels could be estimated.

Biomarkers of Exposure and Effect. Inorganic lead can be measured in blood, serum, urine, cerebrospinal fluid, tissues, bone, teeth, and hair (Aguilera et al. 1989; Blakley and Archer 1982; Blakley et al. 1982; Christoffersson et al. 1986; Delves and Campbell 1988; Ellen and Van Loon 1990; Exon et al. 1979; Hewitt 1988; Jason and Kellogg 1981; Manton and Cook 1984; NIOSH 1977a, 1977d, 1977e, 1977f, 1977g; Que Hee and Boyle 1988; Que Hee et al. 1985a; Rabinowitz et al. 1989; Steenhout and Pourtois 1981; Tabuchi et al. 1989; Tamokuni and Ichiba 1988; Thatcher et al. 1982; Wielopolski et al. 1986; Wilhelm et al. 1989). These measures of lead in body fluids are sensitive and reliable for indicating that background exposures have occurred, as well as higher exposures at which health effects have been observed to occur. Only blood lead levels have been found to be correlated with exposure concentrations. However, blood lead levels are not an exact measure of exposure to lead either because of the transfer, mobilization, and storage among different compartments in the body, and because blood lead does not reflect the entire lead body burden. Because lead cycles between blood and bone, a single blood lead determination cannot distinguish between exposure to a given level for an extended period of time and a previous exposure to a high level that would result in the same blood level due to recycling from bone. Lead levels in tissues, bones, and teeth are generally reliable indicators of lead exposure but are only sensitive at relatively high exposure concentrations. The need exists for the development of a biomarker that would accurately reflect the total body burden from both acute- and chronic-duration at both low and high level exposures.

There is no clinical disease state that is pathognomonic for lead exposure. The neurotoxic effects and hematopoietic effects of lead are well recognized. The primary biomarkers of effect for lead are EP, ALAD, basophilic stippling and premature erythrocyte hemolysis, and presence of intranuclear lead inclusion bodies in the kidneys. Of these, activity of ALAD is the most sensitive indicator of lead exposure (Hernberg et al. 1970; Morris et al. 1988; Somashekaraiah et al. 1990; Tola et al. 1973). Sensitive, reliable, well-established methods exist to monitor for these biomarkers; however, they are not specific for lead exposure. Therefore, there is a need to develop more specific biomarkers of effect for lead.

Absorption, Distribution, Metabolism, and Excretion. Studies of absorption of inhaled lead in adult humans indicate that following deposition of between 30% and 50% of inhaled airborne lead in the respiratory tract, lead is almost completely absorbed (EPA 1986a; Morrow et al. 1980). About 70% of inhaled lead is absorbed within 10 hours. Relatively little is known about the deposition of airborne lead in children because of the lack of data on pediatric respiratory aerosol physiology (EPA 1986a). Although the primary route of exposure for children is oral, more data on the kinetics of deposition and absorption of inhaled lead in children would be useful because secondary occupational exposure to lead dust can be a significant exposure route in families of lead industry workers.

Inhaled lead is absorbed extensively and rapidly by experimental animals as well as humans. Absorption rates of 98% within 7 days in adult rats breathing ^{203}Pb-labeled engine exhaust aerosols have been measured (Morgan and Holmes 1978). Similar results were obtained in studies with other species (Boudene et al. 1977; Griffin et al. 1975b).

Oral intake of lead in humans can result from consuming lead-containing food and beverages and from swallowing lead deposited in the upper respiratory tract after inhalation exposure. The ingestion of lead in children may also occur through normal mouthing activity and pica (abnormal eating behavior). The primary site of lead absorption in children is the gastrointestinal tract because they ingest more lead than adults and because they absorb more lead from this site than adults (Chamberlain et al. 1978). Absorption through this route is about 50% compared with 8% in adults (Chamberlain et al. 1978). Under fasting conditions, adults can absorb as much as 45–80% (Chamberlain et al. 1978). There is an inverse relationship between lead particle size and gastrointestinal absorption (Barltrop and Meek 1979).

The extent of absorption of lead in adult experimental animals (1-15%) is similar to that measured for adult humans (Aungst et al. 1981; Garber and Wei 1974). Similarly, gastrointestinal absorption of lead in experimental animals (rats, monkeys) is also age dependent (Forbes and Reina 1972; Kostial et al. 1978).

Dermal absorption of inorganic lead in humans is not significant (0–0.3% in humans) (Moore et al. 1980). In contrast, alkyl lead compounds have been shown to be rapidly and extensively absorbed through the skin of rabbits and rats (Kehoe and Thamann 1931; Laug and Kunze 1948).

Once absorbed, inorganic lead is distributed in essentially the same manner regardless of the route of absorption (Kehoe 1987). The distribution of lead in man has been well characterized. Lead is not distributed homogeneously; it is distributed into three major compartments: blood, soft tissue, and bone (Rabinowitz et al. 1976). The lead in each compartment has a different rate of intercompartmental movement and residence time. About 95% of the total body burden of lead in humans is found in bones (Barry 1975). There are differences in distribution between children and adults (Barry 1975). Better characterization of these differences would be useful. Transplacental transfer in humans can be demonstrated (Bellinger et al. 1987a; Moore et al. 1982). The physiological stress of pregnancy can mobilize lead from maternal bone, resulting in greater exposure of the fetus (Silbergeld et al. 1988).

Inorganic lead ion in the body is not known to be "metabolized" or biotransformed (EPA 1986a). However, alkyl lead compounds are actively metabolized in the liver by oxidative dealkylation catalyzed by cytochrome P-450 (Bolanowska 1968; EPA 1986a; Kehoe and Thamann 1931). Most of the work on this has been done in animal studies on rats, mice, and rabbits. Following the initial dealkylation step, further metabolism of the intermediates is highly species specific.

In humans and animals, any dietary lead not absorbed by the gastrointestinal tract is excreted in the feces (EPA 1986a). Blood lead that is not retained is excreted by the kidney or excreted through biliary clearance into the gastrointestinal tract (EPA 1986a; Kehoe 1987).

Human infants apparently have a lower total excretion of lead than adults (Rabinowitz et al. 1977; Ziegler et al. 1978). In experimental animals, the relative contribution of the urinary and fecal routes to overall lead excretion is dose and species dependent. In rats, the initial route of excretion is the urine, but as dose increases, the proportion of lead excreted through the bile into the gastrointestinal system increases (Castellino and Aloj 1964; Klaassen and Shoeman 1974; Morgan et al. 1977). Species differences also exist in the rate and extent of total lead excretion (Klaassen and Shoeman 1974).

There is extensive information available on the pharmacokinetics of inorganic lead. However, relatively few human studies address the metabolism of alkyl lead compounds. More information on the toxicokinetics of these compounds would be useful, as they are contributors to the risk for the general population.

Comparative Toxicokinetics. In experimental animals, the relative contribution of the urinary and fecal routes to overall lead excretion is both dose and species dependent (see discussion on "absorption, distribution, metabolism, and excretion" above). Species differences also exist in the rate and extent of total lead excretion. Rats, mice, dogs, and monkeys have been shown to excrete lead at different rates (Boudene et al. 1977; Castellino and Aloj 1974; Keller and Doherty 1980a; Kostial and Momcilovic 1974; Kozlowski and Wojcik 1987; Lloyd et al. 1975;Momcilovic and Kostial 1974; Morgan et al. 1977; Pounds et al. 1978). These studies represent oral, parenteral, and injection exposures; therefore, the apparent species differences may be confounded by exposure route differences. Additional data from directly comparable studies would be useful for clarifying this issue.

The metabolism of alkyl lead compounds appears to begin with dealkylation mediated by cytochrome P-450 in the rat, mouse, and rabbit. This step creates triethyl and trimethyl metabolites from tetraethyl and tetramethyl lead. Further biotransformation of these metabolites is highly species specific (Bolanowska 1968; EPA 1986a; Kehoe and Thamann 1931).

Rats are not known to convert triethyl lead to the diethyl form (Bolanowska 1968), but rabbits excrete large amounts of diethyl lead following exposure to alkyl lead (Klaassen and Shoeman 1974). Final conversion to inorganic lead may take place, although trialkyl lead compounds are usually stable in biological tissues.

2.8.3 On-going Studies

On-going studies regarding the health effects of lead were reported in the Federal Research in Progress File (FEDRIP 1992) database. Table 2-9 presents a summary of these studies.

TABLE 2-9. On-going Studies on Lead[a]

Investigator	Affiliation	Research description	Sponsor
E.X. Albuquerque	University of Maryland, Baltimore, MD	NMDA receptors in lead-induced cognitive deficit (rats)	National Institute of Environmental Health Sciences
B.G. Barisas	Colorado State University, Fort Collins, CO	Molecular mechanisms of heavy metal acute toxicity in cultured mammalian cells	U.S. Department of Agriculture
V. Batuman	Veterans Administration Medical Center, East Orange, NJ	Effect of lead on salt transport in red blood cell	Veterans Administration
C.E. Becker	University of California Berkeley, Berkeley, CA	Human toxicokinetics of trichloroethylene and lead	National Institute of Environmental Health Sciences
D.C. Bellinger	Children's Hospital, Boston, MA	Low-level lead exposure and childhood behavior problems	National Institute of Environmental Health Sciences
D.C. Bellinger	Children's Hospital, Boston, MA	Environmental lead and children's psychologic function (human)	National Institute of Child Health and Human Development
A. Bhattacharya	University of Cincinnati, Cincinnati, OH	Childhood lead exposure and maturation of postural stability and control	National Institute of Environmental Health Sciences
R.E. Bowman	University of Wisconsin, Madison, WI	Cognitive effects of neonatal lead exposure in monkeys (Rhesus macaque)	National Institute of Environmental Health Sciences

TABLE 2-9 (Continued)

Investigator	Affiliation	Research description	Sponsor
D.R. Brown	University Virgin Islands, Charlotte Amalie, VI	Lead as a health hazard in St. Thomas, VI	National Institute oaf General Medical Sciences
J. Burger	Rutgers University, New Brunswick, NJ	Chronic versus critical exposure to lead and neurobehavioral development	National Institute of Environmental Health Sciences
T.F. Campbell	University of Pittsburgh, Pittsburgh, PA	Bone lead level as predictor of speech/language deficits (human)	National Institute on Deafness and Other Communication Disorders
D.O. Carpenter	Wadsworth Center for Labs and Research, Albany, NY	Mechanisms of lead neurotoxicity (aplysia, rats)	National Institute of Environmental Health Sciences
H. Checkoway	University of Washington, Seattle, WA	Semen as a biomarker of effect among lead exposed men	National Institute for Occupational Safety and Health
J. Chisolm	Johns Hopkins University, Baltimore, MD	Safety and efficacy of DMSA for lead poisoning (human)	National Center for Research Resources
D.A. Cory-Slechta	University of Rochester	Behavioral toxicity of lead—Role of the NMDA receptor	National Institute of Environmental Health Sciences
D.A. Cory-Slechta	University of Rochester, Rochester, NY	Behavioral toxicity of lead—a pharmacological analysis (rats)	National Institute of Environmental Health Sciences

TABLE 2-9 (Continued)

Investigator	Affiliation	Research description	Sponsor
M.P. Dieter	National Institute of Environmental Health Sciences	Toxicology studies of lead	National Institute of Environmental Health Sciences
K.M. Dietrich	University of Cincinnati, Cincinnati, OH	Neurobehavioral effects of lead exposure in children—Ten-year follow-up	National Institute of Environmental Health Sciences
W.E. Donaldson	North Carolina State University, Raleigh, NC	Effects of nutrition on responses to environmental contaminants and other mild stressors in neonates	U.S. Department of Agriculture
M.A. Elhelu	University of the District of Columbia, Washington, DC	Environmental lead and its potential health hazard in the District of Columbia	U.S. Department of Agriculture
G. Fosmire	Pennsylvania State University, University Park, PA	Influence of zinc status on aluminum and lead toxicity	U.S. Department of Agriculture
B. Fowler	University of Maryland, College Park, MD	Lead nephropathy and carcinogenesis: Molecular mechanisms	International Lead Zinc Research Organization
D.A. Fox	Montefiore Medical Center, Bronx, NY	Lead toxicity—Effect on cellular calcium homeostasis (rats)	National Institute of Environmental Health Sciences
C. Franklin	Environmental Health Research and Testing, Lexington, KY	Biokinetics of lead in nonhuman primate pregnancy	National Institute of Environmental Health Sciences

TABLE 2-9 (Continued)

Investigator	Affiliation	Research description	Sponsor
D.E. Glotzer	Boston University, Boston, MA	Urinary diuresis and chelation therapy in children	National Center for Research Resources
G.W. Goldstein	Kennedy Research Institute, Inc., Baltimore, MD	Metabolic activity of brain capillaries (rats)	National Institute of Environmental Health Sciences
J.H. Graziano	Columbia University, New York, NY	Environmental lead, reproduction and infant development (human)	National Institute of Environmental Health Sciences
P.B. Hammond	University of Cincinnati, Cincinnati, OH	Health effects of lead on child development	National Institute of Environmental Health Sciences
P.B. Hammond	University of Cincinnati, Cincinnati, OH	Mechanisms underlying lead-induced depression of growth (rat)	National Institute of Environmental Health Sciences
I. Hertz-Picciotto	University of North Carolina Chapel Hill, Chapel Hill, NC	Lead in pregnancy, hypertension and neonatal health (human)	National Institute of Environmental Health Sciences
P.M. Hinkle	University of Rochester, Rochester, NY	Transport and actions of metal ions (human and animal tissue)	National Institute of Environmental Health Sciences
H. Hu	Harvard University, Boston, MA	Determinants of lead levels in mothers and infants (human)	National Institute of Environmental Health Sciences
H. Hu	Harvard University, Boston, MA	Biomarkers of exposure to four heavy metals (human)	National Institute of Environmental Health Sciences

TABLE 2-9 (Continued)

Investigator	Affiliation	Research description	Sponsor
H. Hu	Brigham and Women's Hospital, Boston, MA	The metabolic fate of lead during lactation (human)	National Center for Research Resources
H. Hu	Brigham and Women's Hospital, Boston, MA	Lead, blood pressure, neurologic, and renal function in 2 study populations	National Center for Research Resources
H. Hu	Brigham and Women's Hosptial, Boston, MA	The epidemiology of lead, diet, and blood pressure	National Institute of Environmental Health Sciences
T.E. Jensen	Herbert H. Lehman College, New York, NY	Target sites and compartmentalization in heavy metal exposed cells (yeast)	National Institute of General Medical Sciences
F.C. Kauffman	Rutgers University, New Brunswick, NJ	Influence of lead on nerve growth factor receptor function and expression	National Institute of Environmental Health Sciences
M.J. Kosnett	University of California San Francisco, San Francisco, CA	Vascular effects of chelation in lead exposed workers	National Institute for Occupational Safety and Health
L. Lagunowich	Rutgers University, New Brunswick, NJ	Cerebellar N-cadherin—Is it a target of metal toxicity (mice)	National Institute of Environmental Health Sciences
N.K. Laughlin	University of Wisconsin Madison, Madison, WI	Lead effects on the auditory system in monkeys	National Institute of Environmental Health Sciences

TABLE 2-9 (Continued)

Investigator	Affiliation	Research description	Sponsor
D.A. Lawrence	Albany Medical College of Union University, Albany, NY	Immunotoxicology of heavy metals	National Institute of Environmental Health Sciences
D.B.N. Lee	Veterans Administration Medical Center, Sepulveda, CA	The effect of lead on blood pressure, vascular contractility, and the renin-angiotensin system in the rat	Veterans Administration
H.E. Lowndes	Rutgers University, New Brunswick, NJ	Neurotoxicology of Superfund chemicals	National Institute of Environmental Health Sciences
P.M. Lutz	University of Missouri Rolla, Rolla, MI	Effects of lead on the immune system of children	National Institute of Environmental Health Sciences
R.B. Mailman	University of North Carolina Chapel Hill, Chapel Hill, NC	Lead and development—Immune and brain studies (monkeys)	National Institute of Environmental Health Sciences
R. Masse	Not Specified (France)	Inhalation carcinogenesis in rats exposed to lead oxide	International Lead Zinc Research Organization, Inc.
A.J. McMichael	University of Adelaide, Adelaide, Australia	Biokinetics of lead in human pregnancy	National Institute of Environmental Health Sciences
E. Mejias	Veterans Administration Medical Center, San Juan, PR	The role of lead and uric acid in the nephropathy of gout	Veterans Administration

TABLE 2-9 (Continued)

Investigator	Affiliation	Research description	Sponsor
H.L. Needleman	University of Pittsburgh, Pittsburgh, PA	Attention deficit, school dysfunction, and lead exposure	National Institute of Environmental Health Sciences
E. Nieboer	McMaster University (city, state not specified)	The ion hypothesis of lead carcinogenesis	International Lead Zinc Research Organization, Inc.
J.D. Osterloh	University of California, San Francisco, CA	The effect of parathyroid hormone administration on lead chelation (human)	National Center for Research Resources
J. Peto	Institute for Cancer Research, London, UK	Epidemiology workshop on lead and cancer	International Lead Zinc Research Organization, Inc.
W.N. Piper	University of Michigan, Ann Arbor, MI	Lead and drug toxicity related to heme biosynthesis (rats)	National Institute of Environmental Health Sciences
J.G. Pounds	Wayne State University, Detroit, MI	DMSA action on cellular lead metabolism and toxicity (rat)	National Institute of Environmental Health Sciences
J.G. Pounds	Wayne State University, Detroit, MI	Cellular interactions of lead, calcium, and zinc (rat)	National Institute of Environmental Health Sciences
B. Rajanna	Selma University, Selma, AL	Effects of mercury and lead on phosphoinositidesystem in rat brain	National Institute of General Medical Sciences

TABLE 2-9 (Continued)

Investigator	Affiliation	Research description	Sponsor
J.F. Rosen	Montefiore Medical Center, Bronx, NY	Treatment outcomes in moderately lead toxic children (human)	National Institute of Environmental Health Sciences
J.F. Rosen	Montefiore Medical Center, Bronx, NY	The metabolism of lead in bone (rats, mice, human)	National Institute of Environmental Health Sciences
P.B. Ryan	Harvard University, Boston, MA	Community exposure to lead	National Institute of Environmental Health Sciences
F.A.X. Schanne	Montefiore Medical Center, Bronx, NY	Lead toxicity—Effect on cellular calcium homeostasis (rats)	National Institute of Environmental Health Sciences
L.M. Schell	State University of New York at Albany, Albany, NY	Blood lead in pregnancy/infancy and infant development (human)	National Institute of Environmental Health Sciences
H.M. Shapiro	Howard M. Shapiro, MD, West Newton, MA	A noninvasive test for lead exposure and iron deficiency	National Institute of Environmental Health Sciences
K.R. Shelton	Virginia Commonwealth University, Richmond, VA	Proteins in lead-induced nuclear inclusion bodies (rats)	National Institute of Environmental Health Sciences
R.Z. Sokol	Los Angeles County Harbor-UCLA Medical Center, Torrance, CA	Effects of lead on hypothalamic-pituitary-testiticularaxis (rats, mice)	National Institute of Environmental Health Sciences

TABLE 2-9 (Continued)

Investigator	Affiliation	Research description	Sponsor
B.J. Strupp	Cornell University, Ithaca, NY	Factors modifying behavioral toxicity of lead and PCBs (rats)	National Institute of Environmental Health Sciences
B.J. Strupp	Cornell University, Ithaca, NY	Factors modifying behavioral toxicity of lead and PCBs	U.S. Department of Agriculture
J.B. Suszkiw	University of Cincinnati, Cincinnati, OH	Calcium-surrogate actions of lead ions in secretion (bovine cells)	National Institute of Environmental Health Sciences
T.J. Walsh	Rutgers University, New Brunswick, NJ	Alterations in brain dopamine systems following triethyllead exposure	National Institute of Environmental Health Sciences
R.P. Wedeen	Veterans Administration Medical Center, East Orange, NJ	In vivo tibial XRF measurement of bone lead	Veterans Administration
B. Weiss	University of Rochester, Rochester, NY	Neurobehavioral toxicity of metals (mice)	National Institute of Environmental Health Sciences
J.G. Wetmur	Mount Sinai School of Medicine, New York, NY	Lead toxicity and the ALAD polymorphism (human, mice)	National Institute of Environmental Health Sciences

[a]Derived from FEDRIP (1992)

ALAD = delta-aminolevulinicacid dehydratase; DMSA = dimercaptosuccinic acid; NMDA = N-methyl-D-aspartate; PCBs = polychlorinated biphenyls; XRF = X-ray fluorescence

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

The chemical identities of lead and compounds are given in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical properties of lead and a few of its compounds are listed in Table 3-2. Lead readily tarnishes in the atmosphere but is one of the most stable fabricated metals because of its corrosive resistance to air, water, and soil (Howe 1981). A waste that contains lead or lead compounds may (or may not) be characterized a hazardous waste following testing by the Toxicant Extraction Procedure as prescribed by the Resource Conservation and Recovery Act (RCRA) regulations.

TABLE 3-1. Chemical Identity of Lead and Compounds

Characteristic	Lead[a]	Lead acetate[a]	Lead azide[b]	Lead bromide[c]
Synonym(s)	Lead metal; plumbum; olow (Polish); pigment metal	Lead(2+) acetic acid; plumbous acetate	Initiating explosive (lead azide, dextrinated type only)	No data
Registered trade name(s)	CI77575	Salt of Saturn; Sugar of Lead; Unichem PBA	No data	No data
Chemical formula[b]	Pb	$PbC_4H_6O_4$	PbN_6	$PbBr_2$
Chemical structure	Pb	$[CH_3COO]^- Pb^{2+}$ $[CH_3COO]^-$	$N_3^- Pb^{2+} N_3^-$	$Br^- Pb^{2+} Br^-$
Identification numbers:				
CAS registry	7439-92-1	301-04-2	13424-46-9	10031-22-8
NIOSH RTECS	OF7525000	AI5250000	OF8650000	No data
EPA Hazardous Waste	D008	U144, D008	No data	No data
OHM/TADS	7216776	7217255	No data	No data
DOT/UN/NA/IMCO Shipping	NA	UN 1616, IMO 6.1	No data	No data
HSDB	231	1404	No data	No data
NCI	No data	No data	No data	No data

[a]HSDB 1990
[b]RTECS 1992
[c]Sax and Lewis 1987
[d]RTECS 1990
[e]HSDB 1992

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

TABLE 3-1 (Continued)

Characteristic	Lead chloride[d]	Lead chromate[a]	Lead fluoroborate[e]	Lead iodide[e]
Synonym(s)	Lead(2+) chloride; plumbous chloride	Chromic acid (H_2CrO_4) lead(2+) salt; phoenicochroite and others	Borate(1-), tetrafluoro-, lead(2+); lead borofluoride; lead boron fluoride; lead tetrafluoroborate	Lead diiodide; lead(II) iodide; plumbous iodide
Registered trade name(s)	No data	Canary Chrome Yellow 40-2250; Cologne Yellow; King's Yellow	No data	No data
Chemical formula[b]	$PbCl_2$	$PbCrO_4$	No data	I_2Pb
Chemical structure	$Cl^- Pb^{2+} Cl^-$	$Pb^{2+}[CrO_4]^{2-}$	No data	$I^- Pb^{2+} I^-$
Identification numbers:				
CAS registry	7758-95-4	7758-97-6	13814-96-5	10101-63-0
NIOSH RTECS	OF9450000	GB2975000	ED2700000	OG1515000
EPA Hazardous Waste	No data	D007, D008	D008	D008
OHM/TADS	No data	No data	7217378	No data
DOT/UN/NA/IMCO Shipping	NA 2291	No data	NA 2291; IMO 6.1	NA 2811
HSDB	No data	1650	1991	636
NCI	No data	No data	No data	No data

TABLE 3-1 (Continued)

Characteristic	Lead molybdenum chromate[b]	Lead nitrate[a]	Lead oxide[a]	Lead phosphate[a]
Synonym(s)	Chromic acid, lead and molybdenum salt; lead chromate, sulphate and molybdate; molybdenum-lead chromate; molybdenum orange	Lead dinitrate; nitric acid lead(2+) salt; plumbous nitrate	Lead(2+) oxide; litharge; massicot	Lead(2+) phosphate; Phosphoric acid lead(2+) salt; plumbous phosphate
Registered trade name(s)	C.I. Pigment Red104	No data	CI 77577; CI Pigment Yellow 46	Perlex Paste 500; Perlex Paste 600A; CI 77622
Chemical formula	No data	PbN_2O_6	PbO	$PbPO_4$
Chemical structure	No data	$[NO_3]^- Pb^{2+} [NO_3]^-$	Pb=O	$[PO_4]^{3-} Pb^{2+} Pb^{2+} Pb^{2+} [PO_4]^{3-}$
Identification numbers:				
CAS registry	12709-98-7	10099-74-8	1317-36-8	7446-27-7
NIOSH RTECS	OG1625000	OG2100000	OG1750000	No data
EPA Hazardous Waste	No data	D008	D008	D008, U145
OHM/TADS	No data	7217257	No data	No data
DOT/UN/NA/IMCO Shipping	No data	UN 1469, IMO 5.1	No data	No data
HSDB	No data	637	638	2637
NCI	No data	No data	No data	No data

TABLE 3-1 (Continued)

Characteristic	Lead styphnate[b]	Lead sulfate[d]	Lead sulfide[e]	Tetraethyl lead[e]
Synonym(s)	Initiating explosive lead styphnate; lead trinitroresorcinate; styphnate of lead	Sulfuric acid lead(2+) salt	Lead monosulfide; lead(2+) sulfide; lead(II) sulfide; plumbous sulfide; natural galena	Czteroetylek olowiu (Polish); Lead tetraethide; TEL; tetraethyllead; tetraethylplumbane
Registered trade name(s)	No data	CI 77630; Fast White; Lead Bottoms; Mulhouse White	No data	No data
Chemical formula	$C_6H(NO_2)_3(O_2Pb)$	$PbSO_4$	PbS	$C_8H_{20}Pb$
Chemical structure	No data	$Pb^{2+}[SO_4]^{2-}$	$Pb^{2+}S^{2-}$	$(CH_3CH_2)_4Pb$
Identification numbers:				
CAS registry	63918-97-8	7446-14-2	1314-87-0	78-00-2
NIOSH RTECS	OG6425000	OG4375000	OG4550000	TP4550000
EPA Hazardous Waste	No data	No data	D008	P110; D008
OHM/TADS	No data	No data	7800071	7216922
DOT/UN/NA/IMCO Shipping	No data	UN 1794	NA 2291; IMO 6.1	NA 1649; IMO 6.1
HSDB	No data	No data	639	841
NCI	No data	No data	No data	C54988

TABLE 3-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead[a]	Lead acetate[a]	Lead azide[b]	Lead bromide[b]
Molecular weight	207.20	325.28	291.25	367.04
Color	Bluish-gray	White	White	White
Physical state	Solid	Solid	Needles or powder	Crystalline powder
Melting point	327.4°C	280°C	No data	373°C
Boiling point	1,740°C	No data	Explodes at 350°C[g]	916°C[g]
Density	11.34 g/cm³ at 20°C	3.25 g/cm³ at 20°C	No data	6.66 g/cm³ [k]
Odor	None	Slightly acetic[h]	No data	No data
Odor threshold	No data	No data	No data	No data
Solubility:				
Water	Insoluble	2,210,000 mg/L at 50°C	230 mg/L at 18°C	844,100 mg/L at 20°C[g]
Nitric acid	Soluble	No data	No data	No data
Hot concentrated sulfuric acid	Soluble	No data	No data	No data
Organic solvent(s)	Insoluble	Soluble in glycerol, very slight in alcohol	Acetic acid	No data
Partition coefficients				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	1.77 mmHg at 1,000°C 10 mmHg at 1,162°C 100 mmHg at 1,421°C 400 mmHg at 1,630°C	No data	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	Not flammable	No data	No data
Conversion factors				
Air	None[j]	None[j]	No data	No data
Water	1 ppm(w/v) = 1 mg/L = 1μg/mL	1 ppm(w/v) = 1 mg/L = 1 μg/mL	No data	No data
Solid	1 ppm(w/w) = 1 mg/kg = 1μg/g	1 ppm(w/w) = 1 mg/kg = 1μg/g	No data	No data
Explosive limits	No data	Lead acetate-lead bromate double salt is explosive	No data No data	No data No data
Valence state	0, +2, +4[i]	+2	No data	No data

[a]HSDB 1990
[b]Budavari et al. 1989
[c]Weast 1985
[d]HSDB 1992
[e]Sax and Lewis 1987
[f]Molecular weight calculated from atomic weights
[g]Lide 1992
[h]Sax 1984
[i]Howe 1981
[j]Since these compounds exist in the particulate state, their concentrations are expressed as μg/m³ only.
[k]Temperature not specified

TABLE 3-2 (Continued)

Property	Lead chloride[c]	Lead chromate[a]	Lead fluoroborate[a]	Lead iodide[d]
Molecular weight	278.11	323.22	380.81	461.01
Color	White	Yellow	Colorless	Bright or golden yellow
Physical state	Solid	Solid	Crystalline powder; liquid	Crystals; hexagonal powder
Melting point	501°C	844°C	No data	402°C
Boiling point	950°C	Decomposes[c]	No data	954°C
Density	5.85 g/cm^3 [b]	6.12 g/cm^3 at 15°C	1.75 g/cm^3 at 20°C	6.16 g/cm^3 at 20°C
Odor	No data	No data	Faint odor	Odorless
Odor threshold	No data	No data	No data	No data
Solubility:				
Water	9,900 mg/L at 20°C	0.2 mg/L	No data	630 mg/L at 20°C
Nitric acid	No data	Soluble	No data	No data
Hot concentrated sulfuric acid	No data	No data	No data	No data
Organic solvent(s)	Insoluble in alcohol	Insoluble in acetic acid	No data	Alkali and potassium iodide, aniline, sodium acetate, sodium thiosulfate
Partition coefficients				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	1 mmHg at 547°C[f]	No data	No data	1 mmHg at 479 °C
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	Flammable with combustible organic, or other oxidizable materials	No data	Not flammable
Conversion factors				
Air	None[j]	None[j]	No data	No data
Water	1 ppm(w/v) = 1 mg/L = 1 µg/mL	1 ppm(w/v) = 1 mg/L = 1 µg/mL	No data	No data
Solid	1 ppm(w/w) = 1 mg/kg = 1 µg/g	1 ppm(w/w) = 1 mg/kg = 1 µg/g	No data	No data
Explosive limits	No data	No data	No data	No data
Valence state	+2	+2	No data	No data

TABLE 3-2 (Continued)

Property	Lead molybdenum chromate	Lead nitrate[a]	Lead oxide[a]	Lead phosphate[a]
Molecular weight	No data	331.23	223.21	811.54
Color	No data	Colorless or white	Yellow; reddish-yellow	White
Physical state	No data	Solid	Solid	Solid
Melting point	No data	Decomposes at 470°C	886°C (Litharge); no data (Massicot)	1,014°C
Boiling point	No data	No data	Decomposes at 1,472°C	No data
Density	No data	4.53 g/cm^3 at 20°C	9.3 g/cm^3 (Litharge); 8.0 g/cm^3 (Massicot)[b]	6.9–7.3 g/cm^3 [b]
Odor	No data	Odorless	No data	No data
Odor threshold	No data	No data	No data	No data
Solubility:				
Water	No data	376,500 mg/L at 0°C	10 mg/L at 20°C (Litharge); 23 mg/L at 23°C (Massicot)	Insoluble
Nitric acid	No data	Insoluble	Soluble (Litharge)	Soluble
Organic solvent(s)	No data	1 g in 2,500 mL absolute alcohol 1 g in 75 mL absolute methanol	Soluble in alkali chlorides Soluble in alkali (Massicot)	Soluble in fixed alkali hydroxides
Partition coefficients				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	No data	No data	10 mmHg at 1,085°C	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	Fire risk with organic materials	No data	No data
Conversion factors:				
Air	No data	None[j]	None[j]	None[j]
Water	No data	1 ppm(w/v) = 1 mg/L = 1 μg/mL	1 ppm(w/v) = 1 mg/L = 1 μg/mL	1 ppm(w/v) = 1 mg/L = 1 μg/mL
Solid	No data	1 ppm(w/w) = 1 mg/kg = 1 μg/g	1 ppm(w/w) = 1 mg/kg = 1 μg/g	1 ppm(w/w) = 1 mg/kg = 1 μg/g
Explosive limits	No data	Explosive with easily oxidizable substances, and lead nitrate-lead hypophosphite double salt	2–3 drops 90% peroxyformic acid causes violent explosion	No data
Valence state	No data	+2	+2	+2

TABLE 3-2 (Continued)

Property	Lead styphnate[e]	Lead sulfate[c]	Lead sulfide[e]	Tetraethyl lead[d]
Molecular weight	450.28[f]	303.26	239.26	323.45
Color	Orange-yellow	White	Black, blue, or silvery	Colorless
Physical state	Crystals	Solid	Cubic or metallic crystals: powder	Oily liquid
Melting point	No data	1,170°C	1114°C	-130°C
Boiling point	No data	No data	1281°C (with sublimation)	200°C; 227.7°C (with decomposition)
Density	No data	6.2 g/cm^3 [h]	7.5 g/cm^3 [h]	1.653 g/cm^3 at 20°C
Odor	No data	No data	No data	Musty; pleasant; sweet
Odor threshold	No data	No data	No data	No data
Solubility:				
Water	Insoluble	42.5 mg/L at 25°C	0.86 mg/L at 13°C	0.29 mg/L at 25°C
Nitric acid	No data	No data	Soluble	No data
Hot concentrated sulfuric acid	No data	No data	Soluble	No data
Organic solvent(s)	No data	Insoluble in alcohol[h]	Nitric acid, hot diluted hydrochloric acid[h]	Benzene, ethanol, diethyl ether, gasoline petroleum ether
Partition coefficients				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	No data	No data	10 mmHg at 975°C (solid)	0.2 mmHg at 20°C
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	93°C (closed cup); 85°C (open cup)
Flammability limits	Detonates at 260°C	No data	No data	Lower, 1.8%
Conversion factors:				
Air	No data	None[j]	No data	No data
Water	No data	1 ppm(w/v) = 1 mg/L = 1 µg/mL	No data	No data
Solid	No data	1 ppm(w/w) = 1 mg/kg = 1 µg/g	No data	No data
Explosive limits	No data	No data	No data	No data
Valence state	No data	+2	No data	No data

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Almost all lead-producing mines in the United States are underground operations. Lead obtained as a by-product from open-pit copper mines is the only source of aboveground lead. Mined lead ore is crushed, ground, conditioned, and concentrated (most commonly by flotation). Treatment of lead concentrate involves sintering, smelting, drossing, and refining to 99.95–99.99% purity (Woodbury 1985a). Lead can also be recovered from secondary sources, such as scrap, product wastes, refinery drosses, and residues (U.S. Dept. of Interior 1990). Battery scrap is converted to impure lead or lead alloys by pyrometallurgical processes employing blast, reverberatory, and/or rotary furnaces (Howe 1981).

During 1990, mine production of recoverable lead in the United States was 484,000 metric tons and production of refined lead from primary sources totaled 404,000 metric tons. Lead production by recovery from secondary sources totaled 922,000 metric tons. Old scrap accounted for 94% of total secondary lead production (U.S. Dept of Interior 1992). The available data indicate that secondary lead's share of production has increased significantly since 1977. While the amount of refined lead produced between 1977 and 1990 increased only 3.5%, secondary lead's share of total production increased from 54.4% in 1977 to 68% in 1990 (U.S. Dept of Commerce 1992). Consumption of lead in the United States during 1990 was 1,275,000 metric tons (U.S. Dept of Interior 1991).

During 1989, nine mines in southeastern Missouri produced 89% of the total domestic output of lead ores and concentrates, and lead-producing mines in Idaho, Alaska, and Montana contributed 10.4% of the domestic output. The remainder was a by-product from the mining of other commodities in Arizona, California, Colorado, Idaho, Illinois, Nevada, New Mexico, Tennessee, and Utah. Primary lead was smelted and refined at two plants in Missouri, and one each in Nebraska and Montana. As of 1989, the U.S. secondary lead industry consisted of 42 companies that operated 50 plants with metal refining capacities ranging from approximately 1,000 to 120,000 tons per year. In 1991, one of the two domestic producers of primary lead converted its closed primary smelter in Missouri to a secondary smelter (U.S. Dept. of Commerce 1992). Table 4-1 shows the number of facilities per state that manufacture or process lead and compounds, as well as a range of the maximum amounts of lead present at the facilities.

4.2 IMPORT/EXPORT

During 1990, 93,000 metric tons of lead metal were imported for consumption in the United States. From 1981, when 101,000 tons were imported, to 1990, lead imports rose to a high of 197,000 metric tons and then decreased to the 1990 level. During the same period, net reliance on imports ranged from 7.3% to 16%. U.S. exports of lead metal for 1990 totalled 64,000 metric tons. Between 1981 and 1989, lead exports fluctuated between 4,000 metric tons and 51,000 metric tons before reaching a level only 19,000 metric tons below the level of imports in 1990 (U.S. Dept. of Commerce 1992).

4.3 USE

Lead may be consumed in the form of metal, either pure or alloyed with other metals, or as chemical compounds, primarily oxides. The commercial importance of lead is based on its ease of casting, high density, low melting point, low strength, ease of fabrication, acid resistance, electrochemical reaction with sulfuric acid, and chemical stability in air, water, and soil (Howe 1981).

TABLE 4-1. Facilities That Manufacture or Process Lead[a]

State[b]	Number of facilities	Range of maximum amounts on site in thousands of pounds[c]	Activities and uses[d]
AL	32 (2)[e]	0.1-99,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12
AR	22 (1)[e]	0-49,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13
AZ	12 (3)[e]	1-999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
CA	120 (8)[e]	0-499,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
CO	7 (1)[e]	1-999	1, 2, 4, 5, 6, 7, 8, 9, 13
CT	33 (2)[e]	0-49,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
DE	2	100-999	1, 2, 3, 7, 8
FL	20 (1)[e]	0.1-9,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
GA	33	0-49,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12
HI	1	100-999	8
IA	18	0-999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 13
ID	3	1-999	2, 3, 8, 9
IL	93 (2)[e]	0-499,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
IN	70 (4)[e]	1-49,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
KS	20	1-9,999	1, 3, 4, 7, 8, 9, 11, 13
KY	33 (3)[e]	0-9,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
LA	29	0-49,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 13
MA	41 (3)[e]	0-999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12
MD	12	1-49,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
ME	3	1-999	9
MI	70 (2)[e]	0.1-99,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MN	12 (1)[e]	1-9,999	1, 3, 4, 6, 7, 8, 9, 11, 12
MO	58 (6)[e]	0-499,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MS	24 (1)[e]	0.1-499,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13
MT	4	1-499,999	1, 2, 3, 4, 7, 8
NC	32 (4)[e]	0-9,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
ND	2	1-999	8, 9, 11
NE	12 (2)[e]	0.1-49,999	1, 2, 3, 5, 7, 8, 9, 12
NH	6	1-999	1, 3, 5, 8, 9
NJ	59 (5)[e]	0.1-9,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12
NM	5 (1)[e]	10-9,999	1, 3, 5, 7, 8, 9
NV	4	0.1-999	1, 2, 3, 4, 7, 8, 9, 13
NY	60 (2)[e]	0-49,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13
OH	140 (3)[e]	0-499,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
OK	16	1-49,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12
OR	9 (1)[e]	1-9,999	1, 3, 5, 7, 8, 9, 10, 12, 13
PA	97 (5)[e]	0-499,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
PR	5 (1)[e]	0-99	2, 3, 8, 9, 12
RI	11	1-99,999	1, 2, 3, 4, 8, 9
SC	17	0-9,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
TN	30 (2)[e]	0.1-9,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13
TX	98 (3)[e]	0-49,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
UT	11	1-49,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
VA	23 (4)[e]	0-9,999	2, 3, 5, 6, 7, 8, 9, 12, 13
VI	1	10-99	9, 11

TABLE 4-1 (Continued)

State[b]	Number of facilities	Range of maximum amounts on site in thousands of pounds[c]	Activities and uses[d]
VT	3	10-9,999	1, 2, 3, 7, 9, 12
WA	16	1-49,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
WI	30	0-49,999	1, 4, 5, 7, 8, 9, 10, 12, 13
WV	8	0-999	1, 5, 7, 8, 9, 12

[a]TRI88 1990
[b]Post office state abbreviations used
[c]Data in TRI are maximum amounts on site at each facility.
[d]Activities/Uses:

1. produce
2. import
3. for on-site use/processing
4. for sale/distribution
5. as a byproduct
6. as an impurity
7. as a reactant
8. as a formulation component
9. as an article component
10. for repackaging only
11. as a chemical processing aid
12. as a manufacturing aid
13. ancillary or other use

[e]Number of facilities reporting "no data" regarding maximum amount of the substance on site

The domestic use pattern for lead in 1986 was as follows: transportation was the major end use with about 70% consumed in lead acid batteries, gasoline additives, and other applications. Construction, ammunition, electrical uses, television glass, and paint represented 25%, and 5% was used for ceramics, type metal, ballast or weights, and tubes or containers (U.S. Department of Interior 1987b). The last domestic producer of leaded gasoline additives ceased production in the United States as of early 1991 (U.S. Department of Commerce 1992). According to Section 211 of the CAAA of 1990, "After December 31, 1995, it shall be unlawful for any person to sell, offer for sale, supply, offer for supply, dispense, transport, or introduce into commerce, for use as fuel in any motor vehicle (as defined in section 219[2]) any gasoline which contains lead or lead additives" (CAAA 1990). Despite the decline in lead consumption in most of the uses listed above, lead consumed by the lead-acid battery industry has made up for most of this decline. In 1970, the lead-acid batteries industry consumed 538,000 metric tons or 43.6% of total lead usage. In 1990, however, this industry consumed 1,178,000 metric tons, or 80.0% of domestic consumption. In comparison, leaded gasoline additives and lead oxides accounted for 341,000 metric tons or 27.7% or domestic consumption in 1970 and only an estimated 76,000 metric tons or 6.0% of consumption in 1990 (U.S. Dept of Commerce 1992).

The domestic use pattern for lead in 1990 was as follows: lead-acid storage batteries, used for motor vehicles, motive power, and emergency back-up power, accounted for 80% of total lead consumption. Ammunition, bearing metals, brass and bronze, cable covering, extruded products, sheet lead, and solder represented 12.4%. The remaining 7.6% was used for ceramics, type metal, ballast or weights, tubes or containers, oxides, and gasoline additives (U.S. Dept of Commerce 1992).

Despite these market losses, new uses have been or are being developed that do not present the environmental and health problems associated with some of the old uses of lead. The following list shows some recent and possible new critical uses of lead:

- Lead's advantages in providing protection against radiation exposure have facilitated advances in computers and televisions (which emit gamma rays and X-rays while in operation), medical procedures such as magnetic imaging for diagnostics and many kinds of radiation therapy, and nuclear technology used in a variety of commercial and military applications.

- Lead alloy solder is critical to the transistors, relays, and other components in the printed circuit boards used in all computers and advanced electronic equipment.

- Piezoelectric ceramics, which depend on lead compounds, are used to produce transducers and sensors which make possible ultrasound technologies used in wide-ranging medical and commercial applications, guidance and sensing systems used in defense and commerce, and in addition, new "smart materials" research projects.

- High purity lead oxide is used to make precision glasses needed for lasers, low-dose X-ray machines, fiber optic probes, medical camera systems, and low-light military equipment such as night vision scopes and goggles.

- A new cogeneration technology now being developed outside the United States operates by recirculating molten lead throughout a sealed system. This concept could result in highly efficient energy generation and reduced depletion of fossil reserves.

- Lead-based, high-temperature superconductors are being studied in several research projects. Their superior performance characteristics are expected to facilitate development of new hyperfast computers as well as more sensitive medical diagnostic equipment, more efficient energy delivery systems, and new forms of high-speed surface transportation.

4.4 DISPOSAL

The primary method of disposing of lead is recycling. An estimated 70–75% of the consumed lead in the United States is considered to be recyclable. Certain applications of lead preclude recycling (i.e., use as a gasoline additive). In the United States, 50% of the lead requirements are satisfied by recycled lead products, mostly lead batteries (Howe 1981). Over 90% of the lead used in manufacturing lead-acid storage batteries is recycled within 5 years (Woodbury 1985a). In 1990, 97.8% of all spent lead-acid batteries were recycled (Battery Council International 1992).

A large amount of lead is disposed of annually in municipal and hazardous waste landfills. Lead is commonly disposed of as part of both domestic and commercial lead-containing products (EPA 1982a). Lead-containing waste products include storage batteries, ammunition waste, ordnance, sheet lead, solder, pipes, traps, and other metal products; solid waste and tailings from lead mining; items covered with lead-based paint; and solid wastes created by mineral ore processing, iron and steel production, copper and zinc smelting, and the production and use of various lead-containing products (EPA 1982a; U.S. Department of Interior 1987a). Ammunition and ordnance are the largest contributors to solid waste from lead use activities. They contributed about 50,000 metric tons in 1976, which was about 51% of all identified lead solid waste emissions from use activities (EPA 1982a).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Lead is dispersed throughout the environment primarily as the result of anthropogenic activities. Environmental fate processes may transform one lead compound to another; however, lead is not degraded and is still available for human exposure, even though the compounds containing it vary enormously.

The general population is exposed to lead in ambient air, in many foods, in drinking water, and in dust. Segments of the general population at highest risk of health effects from lead exposure are preschool-age children, pregnant women and their fetuses, and white males between 40 and 59 years of age. Within these groups, relationships have been established between lead exposure and adverse health effects.

Human exposure to lead above baseline levels is common. Some of the more important lead exposures occur as a result of living in urban environments, particularly in areas with high traffic flows, or near stationary emission sources (e.g., smelters), consumption of produce from family gardens, renovation of homes containing lead-based paint, pica (an abnormal eating habit in children), contact with interior lead paint dust, occupational exposure, secondary occupational exposure (e.g., families of workers using lead), smoking, and wine consumption. Higher than normal exposures may also occur to residents living in close proximity to NPL sites that contain elevated levels of lead. The highest and most prolonged lead exposures are found among workers in the lead smelting, refining, and manufacturing industries.

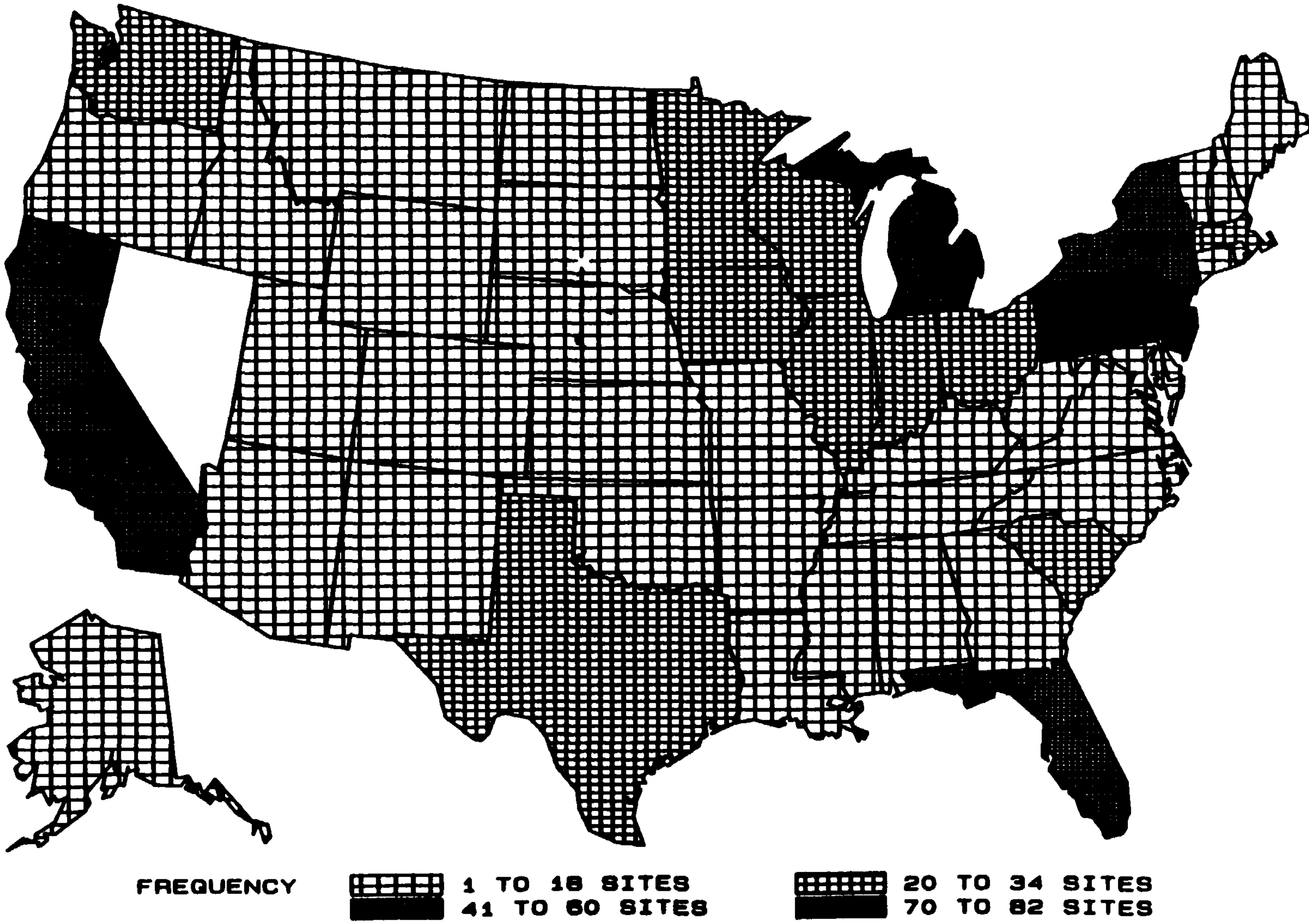
The primary source of lead in the environment is anthropogenic emissions to the atmosphere. As of 1984, combustion of leaded gasoline was responsible for approximately 90% of all anthropogenic lead emissions. EPA has been phasing out the use of lead alkyls in gasoline, however, and as of 1988, auto emissions accounted for only 34% of the annual lead emissions (EPA 1990c). Atmospheric deposition is the largest source of lead found in soils. Lead is transferred continuously between air, water, and soil by natural chemical and physical processes such as weathering, runoff, precipitation, dry deposition of dust, and stream/river flow; however, soil and sediments appear to be important sinks for lead. Lead particles are removed from the atmosphere primarily by wet and dry deposition. The average residence time in the atmosphere is 10 days. Over this time, long-distance transport, up to thousands of kilometers, may take place. Lead is extremely persistent in both water and soil. The speciation of lead in these media varies widely depending upon such factors as temperature, pH, and the presence of humic materials. Lead is largely associated with suspended solids and sediments in aquatic systems, and it occurs in relatively immobile forms in soil.

Lead has been found at 922 of the 1,300 NPL hazardous waste sites (HAZDAT 1992). The frequency of these sites within the United States can be seen in Figure 5-1. Of these sites, 8 are located in the Commonwealth of Puerto Rico (not shown).

5.2 RELEASES TO THE ENVIRONMENT

Lead is a naturally occurring element that has been found in the earth's crust and in all compartments of the biosphere. Although both natural and anthropogenic processes are responsible for the distribution of lead throughout the environment, anthropogenic releases of lead are predominant. Lead is regulated by several federal statutes and is a priority water pollutant and a hazardous air pollutant (see Chapter 7). Although combustion of leaded gasoline used to be the primary source of anthropogenic atmospheric releases of lead, industrial releases to soil from nonferrous smelters, battery plants, and chemical plants

FIGURE 5-1. FREQUENCY OF NPL SITES WITH LEAD CONTAMINATION *



*Derived from HAZDAT 1992

are now major contributors to total lead releases. Of the estimated 81 million pounds of lead or lead compounds released or transferred from industrial facilities that were reported in the Toxics Release Inventory (TRI) in 1988, over 48 million pounds were from primary metals facilities, almost 9 million pounds were from electrical facilities, and over 8 million pounds were from chemical facilities (EPA 1989i). In 1988, 30.8 million pounds of lead and lead compounds were released to the environment and 28.2 million pounds were transferred off-site by the 1,467 facilities reporting to the 1988 TRI (see Table 5-1) (TRI88 1990). A TRI facility is any general manufacturing facility with 10 or more full-time employees that produces, imports, or processes 75,000 or more pounds of any TRI chemical or that uses more than 10,000 pounds of a TRI chemical in a year. The data listed in TRI should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

5.2.1 Air

Of particular importance are emissions of lead to the atmosphere, which is the initial recipient for much of the lead released to the environment. Estimated atmospheric emissions of lead from anthropogenic point and nonpoint sources in the United States during 1989 were estimated to be 7.2×10^3 metric tons (EPA 1991b). Mobile and stationary sources of lead, although found throughout the nation, tend to be concentrated in areas of high population density and near smelters and nonferrous foundries. Natural emissions of lead to the atmosphere from volcanoes and windblown dust are believed to be of minor importance (EPA 1986a).

As indicated in Table 5-2, as of 1989, automotive emissions are no longer the largest source of lead emitted to the atmosphere. More than 90% (mass basis) of automotive lead emissions from leaded gasoline are in the form of inorganic particulate matter (e.g., lead bromochloride [PbBrCl]) and <10% (mass basis) are in the form of organolead vapors (e.g., lead alkyls). The estimated lead emission from automobiles in 1984 was based on an average lead content of 0.44 g lead/gallon gasoline (EPA 1986a); however, as of January 1986, the allowable lead content of leaded gasoline dropped to 0.1 g lead/gallon (EPA 1985g). There has been a 64% reduction in national lead emissions since 1985, primarily as a result of the increased use of unleaded gasoline in catalyst-equipped automobiles. Between January and June of 1990, the actual average lead concentration in leaded gasoline was 0.085 g lead/gallon, indicating consumption of approximately 230,000 kg lead for the production of 2.74 billion gallons of leaded gasoline. During the same 6-month period, 49 billion gallons of unleaded gasoline were produced in the United States (EPA 1990b). While EPA allows up to 0.05 g lead/gallon of unleaded gasoline (EPA 1982b), an analysis of unleaded gasolines conducted in the winter of 1991–1992 indicated that regular grade unleaded gasoline contained, on average, less than 0.0003 g lead/gallon (MVMA 1992).

Reduction trends for air emissions of lead have continued from the late 1970s through the 1980s for both point sources (from 2.9 $\mu g/m^3$ in 1979 to 0.4 $\mu g/m^3$ in 1988) and urban sites (from 0.8 $\mu g/m^3$ in 1979 to 0.1 $\mu g/m^3$ in 1988) (EPA 1990a). The large decrease for point sources results from the use of emission controls for both industrial processes as well as automotive controls, whereas the less dramatic decrease for urban sites is primarily the result of the decreased use of leaded gasoline. In June 1990, unleaded gasoline comprised 94% of all gasoline produced compared with 91% in July 1989 (EPA 1990b), indicating that reductions in urban air lead concentrations should continue as the use of leaded gasoline is phased out. Of the 30.8 million pounds of lead and lead compounds released to the environment from TRI facilities in 1988, 2.59 million pounds were air emissions (see Table 5-1) (TRI88 1990).

No data are available on the amount of lead released to the environment from lead-based paints applied to free-standing structures. The amount of lead in paints sold for consumer use may not exceed 0.06%.

TABLE 5-1. Releases to the Environment from Facilities That Manufacture or Process Lead[a]

		Range of reported amounts released in thousands of pounds[b]						
State[c]	Number of facilities	Air	Underground injection	Water	Land	Total environment[d]	POTW transfer	Off-site waste transfer
AL	32	0-18.2	0-0	0-2.3	0-256.2	0-274.4	0-0.3	0-483.1
AR	22	0-52.8	0-0	0-0.5	0-2.5	0-52.9	0-0.3	0-70
AZ	12	0-162	0-0	0-0.3	0-3,670	0-3,832	0-10	0-16.5
CA	120	0-59.3	0-0	0-0.3	0-350	0-350	0-1.6	0-870
CO	7	0-1.3	0-0	0-0	0-250	0-251.3	0-0.1	0-74
CT	33	0-0.5	0-0	0-1.4	0-0.3	0-1.9	0-0.3	0-324
DE	2	0.1-2.3	0-0	0-0.1	0-0	0.1-2.4	0.1-0.1	0.1-10.3
FL	20	0-10	0-0	0-0.3	0-0.4	0-10.5	0-0.3	0-240
GA	33	0-5.9	0-0	0-0.3	0-0.3	0-5.9	0-0.3	0-198.6
HI	1	0.5-0.5	0-0	0.3-0.3	0.3-0.3	1-1	0-0	0.8-0.8
IA	18	0-3.3	0-0	0-0.3	0-32	0-32.4	0-0.8	0-461.7
ID	3	0-0.3	0-0	0-0	0-0	0-0.3	0-0.8	0-4.4
IL	93	0-22.3	0-0	0-3.1	0-32	0-34.1	0-17	0-815.9
IN	70	0-19	0-0.3	0-11	0-690	0-691	0-0.3	0-503
KS	20	0-3.8	0-0	0-0.3	0-0.3	0-3.8	0-0.8	0-195.6
KY	33	0-8	0-0	0-1.4	0-175	0-177.5	0-1.6	0-193.5
LA	29	0-28.2	0-0	0-4.3	0-100	0-132.5	0-0.3	0-560
MA	41	0-2.4	0-0	0-0.3	0-0.3	0-2.6	0-4.9	0-46.7
MD	12	0-9.6	0-0	0-17.4	0-248.7	0-270.6	0-0.3	0-171.2
ME	3	0.3-0.5	0-0	0-0	0-0	0.3-0.5	0-0	0-23.5
MI	70	0-84.3	0-0	0-9.5	0-95.6	0-106.2	0-1.2	0-127.4
MN	12	0-21.6	0-0	0-1	0-471.1	0-484.5	0-1.1	0-60.8
MO	58	0-339.1	0-0	0-0.8	0-6,427	0-6,766	0-0.8	0-98.2
MS	24	0-6	0-0	0-0.3	0-62	0-62	0-0.3	0-1,090
MT	4	0-84	0-0	0-0.3	0-2,072	0.1-2,156	0-0.1	0-0
NC	32	0-12.3	0-0	0-0.3	0-1	0-12.5	0-0.8	0-24.9
ND	2	0-0.1	0-0	0-0	0-0.1	0-0.1	0-0	0-0.3
NE	12	0-34.6	0-0	0-0.8	0-0.8	0-36.1	0-0.3	0-320
NH	6	0-0.5	0-0	0-0.3	0-0	0-0.8	0-0.1	0-0.1
NJ	59	0-37.7	0-0	0-14.8	0-280	0-285.1	0-58.2	0-409.4
NM	5	0.3-5.7	0-0	0-0.3	0-1,060	0.3-1,066	0-0.3	0-38
NV	4	0-5.3	0-0	0-0	0-12	0-12	0-0	0-0
NY	60	0-19.6	0-0	0-1.1	0-2.5	0-19.6	0-0.8	0-1,457
OH	140	0-19.3	0-0.1	0-51	0-459.7	0-461.3	0-4.4	0-646.2
OK	16	0-4.9	0-0.7	0-0.3	0-1.4	0-5.1	0-0.1	0-29.6
OR	9	0-24.8	0-0	0-0.3	0-0.3	0-24.8	0-0.3	0-360
PA	97	0-44.1	0-0	0-10.1	0-120	0-149.4	0-1	0-558

TABLE 5-1 (Continued)

State[c]	Number of facilities	Range of reported amounts released in thousands of pounds[b]						
		Air	Underground injection	Water	Land	Total environment[d]	POTW transfer	Off-site waste transfer
PR	5	0-11.9	0-0	0-0.5	0-0	0-12.4	0-0	0-0
RI	11	0-7.4	0-0	0-0.3	0-0	0-7.6	0-0.3	0-12.5
SC	17	0-11.4	0-0	0-0.3	0-14.7	0-14.7	0-0.3	0-130.8
TN	30	0-15.3	0-0.1	0-0.3	0-236.5	0-240.9	0-1.1	0-222
TX	98	0-43.3	0-1.2	0-3.7	0-1,167	0-1,210	0-1.5	0-308.9
UT	11	0-48.3	0-0	0-2.6	0-1,500	0-1,550	0-0.3	0-33.5
VA	23	0-14.3	0-0	0-0.3	0-0.2	0-14.5	0-1	0-117.9
VI	1	0-0	0-0	0-0	0.4-0.4	0.4-0.4	0-0	0-0
VT	3	0.1-2.2	0-0	0-0	0-0	0.1-2.2	0.1-0.5	0.3-1.1
WA	16	0-1.8	0-0	0-0.5	0-0.8	0-1.8	0-0.3	0-76
WI	30	0-10	0-0	0-0.3	0-320	0-323.5	0-7.8	0-512
WV	8	0-4.7	0-0	0-9.1	0-0.2	0-9.6	0-0.3	0.3-173.8

[a]TRI88 1990

[b]Data in TRI are maximum amounts released by each facility. Quantities reported here have been rounded to the nearest hundred pounds, except those quantities >1 million pounds which have been rounded to the nearest thousand pounds.

[c]Post office state abbreviation used

[d]The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility

POTW = publicly owned treatment works

TABLE 5-2. National Lead Emission Estimates, 1979-1989[a]

	(Thousand metric tons/year)										
Source category	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989
Transporation	94.6	59.4	46.9	46.9	40.8	34.7	15.5	3.5	3.0	2.6	2.2
Fuel combustion	4.9	3.9	2.8	1.7	0.6	0.5	0.5	0.5	0.5	0.5	0.5
Industrial processes	5.2	3.6	3.0	2.7	2.4	2.3	2.3	1.9	1.9	2.0	2.3
Solid waste	4.0	3.7	3.7	3.1	2.6	2.6	2.8	2.7	2.6	2.5	2.3
Total[b]	108.7	70.6	56.4	54.4	46.4	40.1	21.1	8.6	8.0	7.6	7.2

[a]Derived from EPA 1990c, 1991b

[b]Note: The sums of sub-categories may not equal total because of rounding.

Releases from lead-based paints are frequently confined to the area in the immediate vicinity of painted surfaces, and deterioration or removal of the paint can result in high localized concentrations of lead in indoor air and on exposed surfaces. Sand-blasting procedures to remove paint may disperse lead in the local environment.

The largest volume of organolead vapors released to the atmosphere results from industrial processes such as primary and secondary nonferrous metal smelting, and from the use of leaded gasoline which contains tetraethyl lead as an antiknock additive. These vapors are photoreactive, and their presence in local atmospheres is transitory. Halogenated lead compounds are also formed and ultimately oxides and carbonates (EPA 1985b). Tetraalkyl lead compounds have been found to contribute 5–10% of the total particulate lead present in the atmosphere. Organolead vapors are most likely to occur in occupational settings (e.g., gasoline transport and handling operations, gas stations, and parking garages) and high-traffic areas (Nielsen 1984).

5.2.2 Water

Of the known aquatic releases of lead, the largest ones are from the steel and iron industries and lead production and processing operations (EPA 1982a). In 1988, aquatic releases of lead and lead compounds from TRI facilities totaled 240,014 pounds of lead and 209,468 pounds of lead were released or transferred to publicly owned treatment works (see Table 5-1) (TRI88 1990). Urban runoff and atmospheric deposition are significant indirect sources of lead found in the aquatic environment. Lead reaching surface waters is sorbed to suspended solids and sediments (EPA 1982a).

Although aquatic releases from industrial facilities are expected to be small, lead may be present in significant levels in drinking water. In areas receiving acid rain (e.g, northeastern United States) the acidity of drinking water may increase, thus increasing the corrosivity of the water, which may, in turn, result in the leaching of lead from water systems, particularly from older systems during the first flush of water through the pipes (McDonald 1985). In addition, the grounding of household electrical systems to the plumbing can increase corrosion rates and the subsequent leaching of lead from the lead solder used for copper pipes. Areas where the pH of the water is less than 8.0 may have higher lead drinking water levels as well (Lee et al. 1989).

Lead has been detected in 23% of the surface water samples collected at the NPL hazardous waste sites included in the EPA's Contract Laboratory Program and in 48% of the groundwater samples at geometric mean concentrations in the positive samples of approximately 20 μg/L and 21 μg/L, respectively (CLPSD 1990). Note that the information used from the Contract Laboratory Program Statistical Database includes data from NPL sites only.

5.2.3 Soil

Lead-containing solid wastes are produced primarily as a result of domestic ore production and ammunition use. Other sources include solder, weights and ballasts, bearing metals, and iron and steel production. These sources are concentrated primarily in landfills. For examples, lead has been detected in soil samples taken at an estimated 57% of the NPL hazardous waste sites included in EPA's Contract Laboratory Program Statistical Database at a geometric mean concentration of approximately 44 ppm for the positive samples (CLPSD 1990). Note that the information used from the Contract Laboratory Program Statistical Database includes data from NPL sites only.

In 1988, it was estimated that 28.1 million pounds of lead was transferred off-site rather than released directly to the environment and 28 million pounds of lead were released on-site to land (see Table 5-1) (TRI88 1990).

In 1986, an NPL hazardous waste site was identified in Genesee County, Michigan that contained a landfill and nine surface impoundments. The facility had accepted sludge and residual waste from a chemical warehouse as well as other hazardous wastes. Analysis of the soil, sediments, and water samples taken from the impoundments found lead to be present in sludge samples at a maximum concentration of 11.6 mg/L, in sediment samples at a maximum concentration of 4,770 mg/kg dry weight, in soil samples at 1,560 mg/kg, and in water samples at a maximum concentration of 25 mg/L (EPA 1986d). Thirty of 97 soil samples taken at a former foundry site in Dubuque, Iowa, which was on the NPL, had lead concentrations exceeding 5.0 mg/L as determined using the EP toxicity test (the maximum total lead concentration was 4,890 mg/kg). Most of the positive samples were from soil depths of less than 2.5 feet (Mundell et al. 1989).

Levels of lead found in most soils not impacted by paint emission sources largely reflect atmospheric deposition patterns (EPA 1982a). In some soils, deterioration and removal of lead-based paint from painted surfaces are the primary sources of lead (EPA 1986a).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

In the atmosphere, lead exists primarily in the particulate form. Upon release to the atmosphere, lead particles are dispersed and ultimately removed from the atmosphere by wet or dry deposition. Approximately 40–70% of the deposition of lead is by wet fallout; 20–60% of particulate lead emissions from automobiles are deposited near the source. An important factor in determining the atmospheric transport of lead is particle size distribution. Large particles, particularly those with aerodynamic diameters of >2 μm, settle out of the atmosphere fairly rapidly and are deposited relatively close to emission sources (e.g., 25 m from the roadway after being emitted in motor vehicle exhaust), whereas smaller particles may be transported thousands of kilometers. The dry deposition velocity for lead particles with aerodynamic diameters of 0.06–2.0 μm was estimated to range between 0.2 and 0.5 cm/second in a coniferous forest in Sweden, with an overall particle-size weighted dry deposition velocity of 0.41 cm/second (Lannefors et al. 1983). However, the use of an average net deposition velocity of 0.6 cm/second and an average atmospheric residence time of 10 days has been recommended by the National Academy of Sciences (NAS 1980). The amount of lead scavenged from the atmosphere by wet deposition varies widely; wet deposition can account for 40–70% of lead deposition depending on such factors as geographic location and amount of emissions in the area (Nielsen 1984). An annual scavenging ratio (concentration in precipitation to concentration in air) of 0.18×10^{-6} has been calculated for lead, making it the lowest value among seven trace metals studied (iron, aluminum, manganese, copper, zinc, cadmium), thus indicating that lead is removed from the atmosphere by wet deposition relatively quickly. Wet deposition is more important than dry deposition for removing lead from the atmosphere; the ratio of wet to dry deposition was calculated to be 1.63, 1.99, and 2.50 for sites in southern, central, and northern Ontario, Canada, respectively (Chan et al. 1982). Lead particles from automobile emissions are quite small (<0.1 μm in diameter) but can grow in size by coagulation (Chamberlain et al. 1979). Lead has been found in sediment cores of lakes in Ontario and Quebec, Canada, that were remote from any point sources of lead releases, indicating that long-range atmospheric transport was occurring (Evans and Rigler 1985).

The amount of lead that remains in solution in surface waters depends upon the pH of the water and the dissolved salt content. Equilibrium calculations show that at pH >5.4, the total solubility of lead is approximately 30 μg/L in hard water and approximately 500 μg/L in soft water. Sulfate ions, if present in soft water, limit the lead concentration in solution through the formation of lead sulfate. Above pH 5.4, the lead carbonates, $PbCO_3$ and $Pb_2(OH)_2CO_3$, limit the concentration. The carbonate concentration is in turn dependent upon the partial pressure of carbon dioxide, pH, and temperature (EPA 1986a). In most surface waters and groundwaters, the concentration of dissolved lead is low because the lead will form compounds with anions in the water such as hydroxides, carbonates, sulfates, and phosphates that have low water solubilities and will precipitate out of the water column (Mundell et al. 1989).

A significant fraction of lead carried by river water is expected to be in an undissolved form, which can consist of colloidal particles or larger undissolved particles of lead carbonate, lead oxide, lead hydroxide, or other lead compounds incorporated in other components of surface particulate matters from runoff. Lead may occur either as sorbed ions or surface coatings on sediment mineral particles, or it may be carried as a part of suspended living or nonliving organic matter in water. The ratio of lead in suspended solids to lead in dissolved form has been found to vary from 4:1 in rural streams to 27:1 in urban streams (Getz et al. 1977).

The fate of lead in soil is affected by the specific or exchange adsorption at mineral interfaces, the precipitation of sparingly soluble solid forms of the compound, and the formation of relatively stable organic-metal complexes or chelates with soil organic matter. These processes are dependent on such factors as soil pH, and organic matter content of soil, the presence of inorganic colloids and iron oxides, ion-exchange characteristics, and the amount of lead in soil (NSF 1977). The accumulation of lead in most soils is primarily a function of the rate of deposition from the atmosphere. Most lead is retained strongly in soil, and very little is transported into surface water or groundwater (EPA 1986a; NSF 1977). Lead is strongly sorbed to organic matter in soil, and although not subject to leaching, it may enter surface waters as a result of erosion of lead-containing soil particulates. Lead may be converted to lead sulfate at the soil surface which is relatively soluble when compared with lead carbonate or phosphate. Lead may also be immobilized by ion exchange with hydrous oxides or clays or by chelation with humic or fulvic acids in the soil (Olson and Skogerboe 1975). In soils with pH of ≥5 and with at least 5% organic matter content, atmospheric lead is retained in the upper 2–5 cm of undisturbed soil. Inorganic lead may be bound into crystalline matrices of rocks and remain essentially immobile. Lead complexes and precipitates in soil and their transformation depend on the soil type. In soil with a high organic matter content and a pH of 6–8, lead may form insoluble organic lead complexes; if the soil has less organic matter at the same pH, hydrous lead oxide complexes may form or lead may precipitate out with carbonate or phosphate ions. At a pH of 4–6, the organic lead complexes become soluble and leach out or may be taken up by plants (EPA 1986a). Entrainment of soil particles is another route of lead transport (EPA 1982a). This latter process may be important in contributing to the atmospheric burden of lead around some lead smelting facilities and NPL sites that contain elevated levels of lead in soil.

The downward movement of lead from soil to groundwater by leaching is very slow under most natural conditions except for highly acidic situations (NSF 1977). The conditions that induce leaching are the presence of lead in soil at concentrations that either approach or exceed the cation exchange capacity (CEC) of the soil, the presence of materials in soil that are capable of forming soluble chelates with lead, and a decrease in the pH of the leaching solution (for example, acid rain) (NSF 1977). Partial favorable conditions for leaching may be present in some soils near lead smelting and NPL sites. Leaching of soluble lead from contaminated soils into groundwater may be minimized by the presence of lead carbonate in the soil and maintaining a soil pH of 8–10 (Mundell et al. 1989).

Plants and animals may bioconcentrate lead but biomagnification has not been detected. In general, the highest lead concentrations are found in aquatic and terrestrial organisms that live near lead mining, smelting, and refining facilities; storage battery recycling plants; areas affected by high automobile and truck traffic; sewage sludge and spoil disposal areas; sites where dredging has occurred; areas of heavy hunting (lead source from spent shot); and in urban and industrialized areas. Lead may be present on plant surfaces as a result of atmospheric deposition, whereas its presence in internal plant tissues indicates biological uptake from the soil and leaf surfaces. Although the bioavailability of lead in soil to plants is limited because of the strong absorption of lead to soil organic matter, the bioavailability increases as the pH and the organic matter content of the soil are reduced. Lead is not biomagnified in aquatic or terrestrial food chains. It may contaminate terrestrial plants as a result of atmospheric deposition and uptake from soil, and animals as a result of inhalation of contaminated ambient air or ingestion of contaminated plants. Older organisms tend to contain the greatest body burdens of lead. In aquatic organisms, lead concentrations are usually highest in benthic organisms and algae, and lowest in upper trophic level predators (e.g., carnivorous fish). High bioconcentration factors (BCFs) were determined in studies using oysters (6,600 for Crassostrea virginica), freshwater algae (92,000 for Senenastrum capricornutum) and rainbow trout (726 for Salmo gairdneri), although most median BCF values for aquatic biota are significantly lower: 42 for fish, 536 for oysters, 500 for insects, 725 for algae, and 2,570 for mussels (Eisler 1988). Lead is toxic to all aquatic biota and organisms higher on the food chain may experience lead poisoning as a result of eating lead-contaminated food. Organolead compounds, such as trialkyl and tetraalkyl lead compounds, are more toxic than inorganic forms and have been shown to bioconcentrate in aquatic organisms. Biomagnification of organolead compounds has not been shown and depuration is relatively rapid, with half-life values of 30–45 hours for rainbow trout exposed to tetramethyl lead. Tetraalkyl lead compounds are more toxic than trialkyl lead compounds, and ethyl forms are more toxic than methyl forms (Eisler 1988).

5.3.2 Transformation and Degradation

5.3.2.1 Air

Information available regarding the chemistry of lead in air is limited. Lead particles are emitted to the atmosphere from automobiles as lead halides (mostly $PbBrCl$) and as double salts with ammonium halides (e.g., $2PbBrCl \cdot NH_4Cl$, $Pb_3[PO_4]_2$, and $PbSO_4$ [Biggins and Harrison 1979; Ter Haar and Bayard 1971]). After 18 hours, approximately 75% of the bromine and 30–40% of the chlorine disappear with lead carbonates, oxycarbonates and oxides produced. These lead oxides are subject to further weathering to form increased carbonates and sulfates (Olson and Skogerboe 1975). Lead particles are emitted from mines and smelters primarily in the form of the lead-sulfur compounds, $PbSO_4$, $PbO \cdot PbSO_4$, and PbS (EPA 1986a). In the atmosphere, lead exists primarily in the form of $PbSO_4$ and $PbCO_3$. It is not completely clear how the chemical composition of lead changes during dispersion (EPA 1986a). Monitoring studies indicate that tetraalkyl lead, present in both urban and rural air, may react with hydroxyl ions to form ionic trialkyl and dialkyl species that are more stable in the atmosphere. Relatively recent lead exposure will be by oxides, whereas aged lead surfaces most likely contain carbonates and basic carbonates. Urban air in England that is adverted to rural areas may contain up to 5% of the total lead as alkyl lead; this percentage may increase to 20% for maritime air, with trialkyl lead being the predominant species (Hewitt and Harrison 1987).

Based on the vapor pressure of tetraethyl lead (0.26 mm Hg at 20°C) and tetramethyl lead (26.0 mm Hg at 20°C), these two compounds exist almost entirely in the vapor phase in the atmosphere (Eisenreich et al. 1981). When exposed to sunlight, they decompose rapidly to trialkyl and dialkyl lead compounds and eventually to inorganic lead by a combination of direct photolysis, reaction with hydroxyl radicals, and reaction with ozone. The half-life of tetraethyl lead in summer atmospheres is approximately 2 hours, whereas, the half-life for tetramethyl lead will be on the order of 9 hours. In the winter, both compounds have half-lives of up to several days (DeJonghe and Adams 1986). Trialkyl compounds occur almost entirely in the vapor phase, whereas dialkyl compounds occur almost entirely in particulate form. Because of the relatively high water solubility of trialkyl and dialkyl lead compounds, washout in wet deposition is probably a major process for these compounds. In addition, the dialkyl lead compounds may be significantly removed by dry deposition. Adsorption of tetraethyl and tetramethyl lead to atmospheric particles does not appear to be an important fate process (DeJonghe and Adams 1986; EPA 1985a).

5.3.2.2 Water

The chemistry of lead in aqueous solution is highly complex because this element can be found in a multiplicity of forms. Lead has a tendency to form compounds of low solubility with the major anions found in natural waters. The amount of lead in surface waters is dependent on the pH and the dissolved salt content of the water. The dissolved salt content, in turn, is dependent on the pH and the partial pressure of CO_2 as well as the water temperature. In the environment, the divalent form (Pb^{2+}) is the stable ionic species of lead. Hydroxide, carbonate, sulfide, and, more rarely, sulfate may act as solubility controls in precipitating lead from water. At a pH <5.4, lead sulfate limits the concentration of lead in solution, while at a pH >5.4, lead carbonates limit the lead concentrations (EPA 1979d). The relatively volatile organolead compound, tetramethyl lead, may form as a result of biological alkylation of organic and inorganic lead compounds by microorganisms in anaerobic lake sediments; however, if the water over the sediments is aerobic, volatilization of tetramethyl lead from the sediments is not considered to be important because the tetramethyl lead will be oxidized (EPA 1979d).

In water, tetraalkyl lead compounds are subject to photolysis and volatilization with the more volatile compounds being lost by evaporation. Degradation proceeds from trialkyl lead to dialkyl lead to inorganic lead. Tetraethyl lead is susceptible to photolytic decomposition in water. Triethyl and trimethyl lead are more water-soluble and therefore more persistent in the aquatic environment than tetraethyl or tetramethyl lead. The degradation of trialkyl lead compounds yields small amounts of dialkyl lead compounds. Removal of tetraalkyl lead compounds from seawater occurs at rates that provide half-lives measurable in days (DeJonghe and Adams 1986).

5.3.2.3 Soil

There is evidence that atmospheric lead enters the soil as lead sulfate, or it is converted rapidly to lead sulfate at the soil surface. Many plants commonly take up lead from soil and lead will eventually be returned to soil when these plants decay unless they are harvested or removed (EPA 1986a).

Limited data indicate that tetraethyl and tetramethyl lead are converted into water-soluble lead compounds in soil. Although tetraethyl and tetramethyl lead are not expected to leach significantly through soil, their highly water-soluble metabolites, the trialkyl lead oxides, may be subject to leaching (EPA 1985a).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Lead levels in the ambient air have been monitored in a number of remote, urban, and nonurban areas of the United States and other countries (EPA 1986a). Atmospheric lead concentrations vary widely but usually decrease with vertical and horizontal distance from emission sources; they are generally 0.3–0.8 times lower indoors than outdoors, with an average ratio of 0.5. Levels of lead in ambient air range from 7.6×10^{-5} $\mu g/m^3$ in remote areas such as Antarctica (Maenhaut et al. 1979) to >10 $\mu g/m^3$ near stationary sources such as smelters, with an average annual concentration of below 1.0 $\mu g/m^3$ for urban monitoring sites. Unusually high levels may be found in areas of high traffic density and in confined places, such as parking garages and tunnels, where leaded auto exhaust is found. Monitoring data from a composite of 147 sampling sites throughout the United States indicate that the maximum quarterly average lead level in urban air during 1984 was 0.36 $\mu g/m^3$ and 0.2–0.4 $\mu g/m^3$ in 1986 (EPA 1988f, 1989h). Between 1979 and 1983, atmospheric lead concentrations in precipitation in Minnesota decreased from 29 to 4.3 $\mu g/L$ at urban locations and from 5.7 to 1.5 $\mu g/L$ at rural locations, indicating a reduction in lead emissions of more than 80%. This reduction resulted primarily from the decreased use of leaded gasoline (down 56%) and the use of more efficient emission controls on other sources (Eisenreich et al. 1986).

In the 1960s, the National Air Surveillance Network (NASN) was established to monitor ambient air quality levels of total particulate solids and trace metals, including lead, at sites in larger American cities. In 1981 some old sites were eliminated and new ones were added to give 139 urban sites for air monitoring purposes. In 1988, the average lead concentration for all 139 sites was 0.085 $\mu g/m^3$, well below the National Ambient Air Quality Standard of 1.5 $\mu g/m^3$ that has been recommended for lead (EPA 1990c). In 1988, the average concentration of 18 point-source sites was 0.4 $\mu g/m^3$, down from 2.9 $\mu g/m^3$ in 1979, and the average concentration for urban sites was 0.1 $\mu g/m^3$, down from 0.8 $\mu g/m^3$ in 1979 (EPA 1990c). This was thought to be caused by decreased use of leaded gasolines.

5.4.2 Water

Lead has been monitored in surface water, groundwater, and drinking water, and in sediments throughout the United States and other countries. The concentration of lead in surface water is highly variable depending upon sources of pollution, lead content of sediments, and characteristics of the system (pH, temperature, etc.). Mean levels of lead in surface water measured at 50,000 surface water stations throughout the United States are 3.9 $\mu g/L$ (based on 39,490 occurrences) (Eckel and Jacob 1988), although levels as high as 890 $\mu g/L$ have been measured (EPA 1986a). Lead is estimated to be present in sea water at approximately 0.005 $\mu g/L$ (EPA 1982a). Lead concentrations in surface water are higher in urban areas than in rural areas (EPA 1982a).

Sediments contain considerably higher levels of lead than corresponding surface waters. The average lead content of river sediments is estimated to be approximately 20,000 $\mu g/g$, whereas the average level in coastal sediments is approximately 100,000 $\mu g/g$ (EPA 1982a). Surface sediment concentrations in Puget Sound ranged from 13 $\mu g/g$ to 53 $\mu g/g$ (Bloom and Crecelius 1987). An analysis of sediments taken from 10 lakes in Pennsylvania indicated that the elevated lead values were not derived from leaching of lead from the native rocks as a result of acid deposition, but rather originated from anthropogenic lead deposition (probably from automotive emissions) on the soil surface and subsequent runoff of soil particulates into the lake (Case et al. 1989).

Based on a survey of 900 public water supply systems, EPA (1988b) estimated that 99% of the 219 million people in the United States using public water supplies are exposed to drinking water with levels of lead <5 μg/L and approximately 2 million people are served by drinking water with levels of lead greater than 5 μg/L. A survey of 580 cities in 47 states indicated that the national mean concentration of lead in drinking water was 29 μg/L after a 30-second flushing period (EPA 1988f, 1989h); however, it was estimated that in 1988 the average lead content of drinking water was 17 μg/L (Cohen 1988b). In 1986, the Safe Drinking Water Act Amendments banned the use of lead solder or flux containing more than 0.2% lead and the use of lead pipes or fittings that contained more than 8% lead (EPA 1988f, 1989h).

Lead levels ranging between 10 and 30 μg/L can be found in drinking water from households, schools, and office buildings as a result of plumbing corrosion and subsequent leaching of lead. The combination of corrosive water and lead pipes or lead-soldered joints in either the distribution system or individual houses can create localized zones of high lead concentrations that exceed 500 μg/L (EPA 1989f).

A survey of 1,484 drinking water samples taken from various districts of the American Water Works Service Company showed that average lead levels in a 1-liter first-draw sample for copper, galvanized, and plastic pipes were 9, 4.2, and 4.5 μg/L, respectively. These data show that even plumbing that did not use lead solder for copper pipes (e.g., plastic pipes) contained significant levels of lead, primarily from the brass faucet fixtures which are used in almost all plumbing. The brass fixtures may account for approximately one-third of the lead in the first-draw water (Lee et al. 1989).

5.4.3 Soil

The natural lead content of soil derived from crustal rock, mostly as galena (PbS), typically ranges from <10 to 30 μg/g soil. However, the concentration of lead in the top layers of soil varies widely due to deposition and accumulation of atmospheric particulates from anthropogenic sources. The concentration of soil lead generally decreases as distance from contaminating sources increases. Next to roadways, it is estimated that the levels of lead in the upper layer of soil are typically 30–2,000 μg/g higher than natural levels, although these levels drop exponentially up to 25 m from the roadway (EPA 1986a). Soil adjacent to a smelter in Missouri had lead levels in excess of 60,000 μg/g (Palmer and Kucera 1980). Soils adjacent to houses with exterior lead-based paints may have lead levels of >10,000 μg/g (EPA 1986a). Extractable lead in surface soil samples (0–5 cm depth) from an agricultural area near a car battery manufacturing plant (taken at 0.3 km from the source) decreased from 117 μg/g to 1 μg/g within 1 year after the plant stopped operating as a result of lead reactions with the soil (Schalscha et al. 1987). Soil collected by scraping the top 2.5 cm of soil surface near homes and streetside in Louisiana and Minnesota contained median lead concentrations of greater than 840 μg/g in New Orleans and 265 μg/g in Minneapolis, whereas the small towns of Natchitoches, Louisiana and Rochester, Minnesota, had soil lead concentrations of less than 50 μg/g and 58 μg/g, respectively, suggesting that lead contaminated soil is a major source of lead exposure in urban areas (Mielke 1992).

Studies carried out in Maryland and Minnesota indicate that within large light-industrial urban settings such as Baltimore, the highest soil lead levels generally occur in inner-city areas, especially where high traffic flows have long prevailed (Mielke et al. 1983, 1985, 1989) and that the amount of lead in the soil is correlated with the size of the city (Mielke 1991). In 1981, soil lead levels in the Minneapolis/St. Paul inner-city area were 60 times higher (423 μg/g) than levels found in rural Minnesota (6.7 μg/g), with almost all the increase (95%) resulting from the combustion of leaded gasoline. A study conducted in Minneapolis, Minnesota after the lead content of gasoline has been significantly reduced, found that median soil lead levels taken from the foundations of homes, in yards, and adjacent to the street were 700 μg/g, 210 μg/g, and 160 μg/g, respectively; comparable samples taken from the smaller city of Rochester, Minnesota showed that the median soil lead concentrations did not exceed 100 μg/g at any location tested (Mielke et al. 1989). The Minneapolis data showed that average lead levels were elevated in soil samples taken from the foundations of homes, but that lead levels were low (<50 μg/g) in areas where children could be expected to play such as parks that were located away from traffic but were higher in play areas around private residences. Soil samples taken from around the foundations of homes with painted exteriors had the highest lead levels (mean concentrations of 522 μg/g) but levels around homes composed of brick or stucco were significantly lower (mean concentration 158 μg/g) (Schmitt et al. 1988). Severely contaminated soils were located near house foundations adjacent to private dwellings with exterior lead-based paint, at levels up to 20,136 μg/g. Elevated soil lead concentrations were found in larger urban areas with 27%, 26%, 32%, and 42% of the soil samples exceeding 300 μg/g lead in Duluth, inner-city North Minneapolis, inner-city St. Paul, and inner-city South Minneapolis, respectively. Only 5% of the soil samples taken from the smaller urban areas of Rochester and St. Cloud, Minnesota, had lead levels in excess of 150 μg/g. It is suggested that the higher lead levels associated with soils taken from around painted homes in the inner city are the result of greater atmospheric lead content, resulting from the burning of leaded gasoline in cars and the washdown of building surfaces to which the small lead particles adhere by rain (Mielke et al. 1989).

In the state of Maine, soil samples taken from areas of high risk (within 1–2 feet of a foundation of a building more than 30 years old) indicated that 37% of the samples had high lead concentrations (>1,000 μg/g). Forty-four percent of the private dwellings had high lead levels in the soil adjacent to the foundation, whereas only 10% of the public locations (playgrounds, parks, etc.) did. In addition, the largest percentage (54%) of highly contaminated soil was found surrounding homes built prior to 1950, whereas homes built after 1978 did not have any lead contamination in the soil (Krueger and Duguay 1989). In the Cincinnati prospective lead study of public and private low- and moderate-income housing, the lead concentration ranges were as follows: painted interior walls, 0.1–35 mg/cm^2; interior home surface dust, 0.04–39 mg/m^2 and 72–16,200 μg/g; interior home dustfall, 0.0040–60 mg/m^2/30 days; exterior dust scrapings, 20–108,000 μg/g; and dust on children's hands, 1–191 μg, with the lead levels in older private deteriorating or dilapidated housing being higher than the levels in newer public and rehabilitated housing (Clark et al. 1985).

5.4.4 Other Environmental Media

Lead has been detected in a variety of foods. Typical concentrations of lead in various foods are (EPA 1986a):

Food group	Concentration (μg/g)
Dairy products	0.003–0.083
Meat, fish, and poultry	0.002–0.159
Grain and cereal products	0.002–0.136
Vegetables	0.005–0.649
Fruit and fruit juices	0.005–0.223
Oils, fats, and shortenings	0.002–0.028
Sugar and adjuncts	0.006–0.073
Beverages	0.002–0.041 (μg/L)

Canning foods in lead-soldered cans may increase levels of lead by 8–10-fold; however, the impact of canning appears to be decreasing as a result of a decrease in the use of lead-soldered cans. The use of three-piece lead-soldered cans ceased in 1991; however, older lead-soldered cans may still be present in some households. In 1974, for example, the lead level in evaporated milk in lead-soldered cans was 0.12 μg/g, whereas in 1986, after these cans were phased-out, the lead level in evaporated milk dropped to 0.006 μg/g (Capar and Rigsby 1989). The lead content in canned foods dropped from an overall mean of 0.31 ppm in 1980 to 0.04 ppm in 1988 (NFPA 1992). A 1982 Canadian study indicated average lead concentrations in dairy milk to be 0.00112 μg/g, whereas lead levels in various infant formulas ranged from 0.0026 μg/g for bottled water to 0.0737 μg/g in infant formula powders (Dabeka and McKenzie 1987). Additional exposure to lead through dietary intake by people living in an urban environment is estimated to be approximately 28 μg/day for adults and 91 μg/day for children, all of which can be attributed to atmospheric lead (dust). Atmospheric lead may be added to food crops in the field or garden (through uptake from soil and from direct deposition onto crop surfaces), during transport to market, processing, and kitchen preparation (EPA 1986a).

Lead may leach from lead crystal decanters and glasses into the liquids they contain. Port wine which contained an initial concentration of 89 μg/L lead, was stored for 4 months in crystal decanters containing up to 32% lead oxide. At the end of 4 months lead concentrations in the port were 5,331, 3,061, and 2,162 μg/L in decanters containing 32%, 32%, and 24% lead oxide, respectively. Lead was also found to elute from lead wine glasses within minutes. Mean lead concentrations in wine contained in 12 glasses rose from 33 μg/L initially to 68, 81, 92, and 99 μg/L after 1, 2, 3, and 4 hours, respectively (Graziano and Blum 1991).

Flaking paint, paint chips, and weathered powdered paint, which are most commonly associated with deteriorated housing stock in urban areas, are major sources of lead exposure for young children residing in these houses, particularly for children with pica (i.e., the compulsive, habitual consumption of nonfood items) (Bornschein et al. 1986; EPA 1986a). Lead concentrations of 1,000–5,000 $\mu g/cm^2$ have been found in chips of lead-based paint (Billick and Gray 1978), suggesting that consumption of a single chip of paint would provide greater short-term exposure than any other source of lead (EPA 1986a). It is estimated that between 40 % and 50% of currently occupied housing in the United States may contain lead-based paint on exposed surfaces (Chisolm 1986).

Lead is also present in tobacco at concentrations of approximately 2.5–12.2 μg/cigarette, of which approximately 2–6% may actually be inhaled by the smoker (WHO 1977).

Cases of lead poisoning have been related to less common sources of exposure. Illicit "moonshine" whiskey made in stills composed of lead-soldered parts (e.g., truck radiators) may contain high levels of lead. Seven of 12 samples of Georgia moonshine whiskey had detectable levels of lead with a maximum concentration of 5.3 mg/L (Gerhardt et al. 1980). Use of lead ammunition may result in exposure to lead dust generated during gun or rifle discharge at levels up to 1,000 $\mu g/m^3$ (EPA 1985c), lead pellets ingested or imbedded in animals that are used as food sources, and lead pellets imbedded in humans from shooting incidents (Johnson and Mason 1984).

In 1972, household dust samples taken near nonferrous ore smelters in El Paso, Texas, which were known to emit 1,012 metric tons of lead per year, had lead levels of 22,191 μg/g (geometric mean) and 973 μg/g at distances from the smelter of 1.6 km and 6.4 km, respectively (Landrigan and Baker 1981).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Information on occupational exposure to lead is obtained primarily from the National Occupational Exposure Survey (NOES) and industry surveys of workers. While occupational exposure is widespread, environmental monitoring data on levels of exposure in many occupations are not available. A permissible exposure limit (PEL) of 50 $\mu g/m^3$ for workplace air has been established for lead by the OSHA (29 CFR 1910.1025). The NIOSH has estimated that more than 1 million American workers were occupationally exposed to inorganic lead in greater than 100 occupations (NIOSH 1977a, 1978f). The NOES, conducted by NIOSH between 1980 and 1983, estimated that 25,169 employees were exposed to tetraethyl lead; approximately 57,000 employees were exposed to various lead oxides mostly in non-ferrous foundries, lead smelters, and battery plants; 3,902 employees were exposed to lead chloride; and 576,579 employees were exposed to some other form of lead in the workplace in 1980 (NIOSH 1990).

Potentially high levels of lead may occur in the following industries: lead smelting and refining industries, battery manufacturing plants, steel welding or cutting operations, construction, rubber products and plastics industries, printing industries, firing ranges, radiator repair shops and other industries requiring flame soldering of lead solder, and gas stations (EPA 1986a; Feldman 1978; Goldman et al. 1987; NIOSH 1978a). In these work areas, the major routes of lead exposure are inhalation and ingestion of lead-bearing dusts and fumes. Airborne dusts settle onto food, water, clothing, and other objects, and may subsequently be transferred to the mouth. Therefore, in these occupational areas, good housekeeping and good ventilation have a significant impact on the extent of worker exposure. Workers involved in the production of gasoline additives, tetraethyl lead and tetramethyl lead, are exposed to both inorganic lead and alkyl lead. The major potential hazard to these workers appears to be from dermal exposure since alkyl leads may be absorbed through the skin (EPA 1986a). Others who may be occupationally exposed to lead are artists and craftsmen who may be exposed to lead used in paints, ceramic glazes, and lead solder for sculpture and stained glass (Hart 1987) and welders where lead concentrations in the welding fumes generated by gas metal arc welding of carbon steel ranged from 1.0 to 17.6 $\mu g/m^3$, well below the established PEL for the workplace (Larson et al. 1989).

Lead exposure is frequently monitored by biological testing (e.g., determination of urinary lead levels, blood lead levels, urinary coproporphyrin levels, or ALA levels) rather than monitoring the workplace environment for lead concentrations (EPA 1986a; NIOSH 1978a). A recent employer survey of California industries that use lead indicated that 229,434 employees were potentially exposed to lead in the workplace; of these workers, 59,142 (25%) had received routine biological monitoring (i.e., determination of blood lead levels), and only 24,491 (10%) were in positions where environmental monitoring (workplace air lead levels) had ever been conducted. In addition, approximately 12% of the potentially exposed individuals were in the construction industry which does not require air or blood monitoring (Rudolph et al. 1990). Workers in an electronic components plant that makes ceramic-coated capacitors and resistors using leaded glass for the ceramic coating were found to be exposed to ambient lead levels ranging from 61 to 1,700 $\mu g/m^3$ and to have blood lead levels ranging from 16 to 135 $\mu g/dL$. Approximately 30% of the workforce was found to be on medical leave as a result of their blood lead levels exceeding 40 $\mu g/dL$; an analysis of blood lead levels among family members of the exposed workers gave mean levels of 10.2 $\mu g/dL$ compared with 6.2 $\mu g/dL$ for families of nonexposed workers (Kaye et al. 1987).

Exposure of the general population to lead is most likely to occur through the ingestion of contaminated food and drinking water, and by the inhalation of lead particulates in ambient air. Direct inhalation of lead accounts for only a small part of the total human exposure, however, lead that is adsorbed to soil may be inhaled as dust and reentrainment of lead-contaminated dust is common. Fruits, vegetables, and grains may contain levels of lead in excess of background levels as a result of direct deposition of lead onto plant surfaces and by plant uptake of lead from soils (EPA 1986a).

In 1982–83, the baseline value for daily intake of lead by inhalation in a nonurban environment was estimated to be 0.5 μg/day for a 2-year-old child, 1.0 μg/day for an adult working indoors, and 2.0 μg/day for adults working outdoors based on an average atmospheric lead concentration of 0.1 $\mu g/m^3$ and an indoor/outdoor lead concentration ratio of 0.5. In an urban environment, the indoor/outdoor ratio was assumed to be approximately 0.8 to give a lead exposure estimate of 1.0 $\mu g/m^3$ for adults assuming a 2-hour/day exposure to an outside lead concentration of 0.75 $\mu g/m^3$, a 20-hour/day exposure to an indoor lead concentration of 0.6 $\mu g/m^3$, a 2-hour/day exposure to 5 $\mu g/m^3$ in high traffic, and an average daily intake of air by an adult of 20 m^3. This indicates that urban and nonurban residents inhaled approximately the same amount of lead dust (EPA 1986a). Drastic reductions in the lead content of gasoline since 1986 have resulted in a 64% decrease in lead emissions to the atmosphere (see Section 5.4.1). As a result, the current baseline level of lead intake by inhalation may be markedly lower than 1986 levels.

Based on data from the FDA's Total Diet Food Studies, baseline values for average daily intake of lead by consumption of food, water, and beverages are presented in Table 5-3. The Total Diet Food Studies conducted between 1982 and 1988, determined daily intakes of a variety of pesticides, industrial chemicals, and elements for eight age and sex groups. In 1984, lead residues were found in 193 of the 201 foods analyzed. A comparison of daily intakes of lead by age group (6 months, 2 years, and adults) showed that lead intakes dropped by approximately 50% for each group between 1980 and 1984 (Gunderson 1988) and continued to decrease through 1990 for all age and sex groups (FDA 1992b; Bolger et al. 1991). Preliminary data from the 1989–1990 Total Diet Survey indicate that dietary lead intake now ranges from 5 to 11 μg/day for all age groups combined, primarily as a result of reduced lead solder in cans and the phase-out of leaded gasoline. Further reductions in lead exposure will be more difficult to identify and achieve (Bolger et al. 1991). It was noted that during the 1980s, the average blood lead levels in U.S. children dropped from 17 μg/dL to 4–6 μg/dL (EPA 1991d). FDA estimated that in 1990, toddlers (2-years old) received 16% of their total lead exposure from food (5 μg/day), 1% from soil, 7% from water, and 75% from dust. A study of lead in the diet of Canadian infants found an average intake by children 0–1 years of age to be 16.5 μg/day when both food and water ingestion were considered (Dabeka and McKenzie 1988). EPA estimated that in 1990 lead intake from U.S. drinking water would be 11.9 μg/day for a 6-year-old child and 7.5 μg/day for an infant less than 1 year old (Cohen 1988b).
Between 1979 and 1989 there was a virtual elimination of the use of lead-soldered food cans, with a concomitant drop in lead levels in food. Average daily intakes of lead for adults, based on an analysis of 27 market basket samples taken nationwide for a 1980–1982 Total Diet Study, were as follows (Gartrell et al. 1986b):

Food group	Average adult intake (μg/day)
Dairy products	4.54
Meat, fish, and poultry	4.09
Grain and cereal products	9.84
Potatoes	1.39
Leafy vegetables	0.94
Legume vegetables	9.18
Root vegetables	1.39
Garden fruits	4.44
Fruits	10.0

Food group	Average adult intake (μg/day)
Oils and fats	1.23
Sugar and adjuncts	2.34
Beverages	6.86
Total lead intake	56.5

This value is only slightly higher than the estimated lead intake of 54 μg/day found in a Canadian 24-hour duplicate diet study conducted during 1981. The average lead content of the 10 food groups samples ranged from 0.088 μg/g for drinking water to 0.654 μg/g for cheese (Dabeka et al. 1987).

Plastic food wrappers may be printed with pigments that contain lead chromates. Plastic wrappers used for 14 different national brands of bread collected in New Jersey contained a mean concentration of 26 mg of lead for a bag size of 2000 cm^2. A survey of 106 homemakers who buy such breads indicated that 39% of them reused the bags and 16% of the respondents turned the bags inside out to reuse them, suggesting that the potential exists for lead leaching from the paint into the stored food (Wiesel et al. 1991).

An analysis of 210 human milk samples showed a mean lead level of 1.04 ng/g (range: <0.05–15.8 ng/g). Women who resided in homes that were more than 30 years old, lived in high-traffic areas for more than 5 years, or had drunk three or more cups of coffee in the preceding 24 hours prior to taking the milk sample, had higher lead levels. The increased lead levels resulting from coffee drinking were thought to be the result of mobilization by the coffee of the lead stored in tissues and bone (Dabeka et al. 1988).

The American Academy of Pediatrics (1987) has concluded that lead continues to be a significant hazard to the health of children in the United States because most children in this country are exposed to lead due to contamination of air, dust, and soil through combustion of leaded gasoline. In addition, many children are at risk for ingestion of lead-based paint and of soil and dust contaminated through the deterioration of lead-based paint. While a 1974 study indicated that elevated blood lead levels in children were most likely to result from ingestion of lead-contaminated soil and that the most likely source of the lead was lead-based paint rather than lead from automotive exhaust (Ter Haar and Aronow 1974), subsequent data has shown that children with the highest blood lead levels live in areas with high traffic flow where lead particles in the air may fall directly to the soil or adhere to the outer surfaces of building and be washed to the soil with rain (Mielke et al. 1989). Studies of children in Minnesota showed that blood lead levels in children were correlated with soil lead levels which were highest in inner-city areas; soil lead levels and blood lead levels were not correlated with the age of housing, although the presence of lead-based paint or lead abatement procedures may be of significance for individual children (Mielke et al. 1989). EPA (1989c) uses 0.2 g/day as a typical soil ingestion rate (including both dirt and dust) for children 1–6 years of age.

Lead intoxication has been observed in children but rarely in adults in a residential setting (Sedman 1989). More than 1.2 million children less than 6 years of age are estimated to have blood lead levels that exceed 15 μg/dL as a result of living in deteriorated housing with lead paint; 188,000 children may have blood lead levels that exceed 25 μg/dL. It is estimated that the number of children with blood lead levels below 15 μg/dL would almost double between 1985 and 1990 as a result of the decrease in the amount of lead in leaded gasoline to a maximum 0.1 g/gal in 1988. An estimated 233,000 children are exposed to lead from stationary sources (out of a total exposed population of 2.24 million people). In all, as many as

TABLE 5-3. Daily Average Intake of Lead (μg Lead/Day) [a]

		Year					
Age	Sex	1980	1982	1984	1986	1988	1990
6–11 months	Male/ Female	~34	20	16.7	10	5	3.8
2 years	Male/ Female	~45 No data	25.1 No data	23.0 No data	12.8 No data	5.0 No data	4.3 No data
14–16 years	Female	No data	No data	28.7	15.2	6.1	6.1
14–16 years	Male	No data	No data	40.9	21.8	8.2	8.5
25–30 years	Female	No data	32.0	28.7	14.8	7.9	6.7
25–30 years	Male	84	45.2	40.9	21.2	10.0	8.5
60–65 years	Female	No data	No data	30.4	15.6	No data	2.2
60–65 years	Male	No data	No data	37.6	19.1	No data	8.1

[a]Derived from Gunderson 1988; Bolger 1991; FDA 1992.

11.7 million children less than 7 years old are exposed to lead in dust and soils from a variety of sources: 5.9 million children are exposed from lead paint; 5.6 million children are exposed from leaded gasoline and lead emissions in cities; and 0.2 million children are exposed from stationary emission sources such as smelters and battery plants. In addition, 6.6 million children may be at risk from exposure to lead in drinking water as a result of lead solder and pipes used in plumbing (Mushak and Crocetti 1989).

The lead content of dusts can be a significant source of exposure, particularly for young children. Baseline estimates of potential human exposure to dusts including intake due to normal hand-to-mouth activity are 0.2 g/day for children 1–6 years old and 0.1 g/day for adults when both indoor and outdoor ingestion of soil including dust are considered (EPA 1989c). It is believed that ingestion of dust by children most commonly occurs as the result of the mouthing of hands, toys, and food that have come into contact with lead-containing surface dust, and less commonly by deliberate ingestion of soil (Bornschein et al. 1986). Although ingestion of lead-containing paint may lead to elevated blood lead levels in young children, the major source of moderately elevated blood lead levels (30–80 μg/dL) in inner city children is mostly likely to be contaminated household dust and subsequent hand contamination and repetitive mouthing (Charney et al. 1980). Lead levels of indoor dust and outdoor soil were found to be strongly predictive of blood lead levels in over 200 urban and suburban infants followed from birth to 2 years of age; however, the blood lead levels were not correlated with indoor air or tap water lead levels, nor the size of nearby roadways. Indoor dust lead levels and soil lead levels in the homes of children with high blood lead levels (>8.8 μg/dL) were 72 μg/wipe (windowsill dust) and 1,011 μg/g, respectively; children with low blood lead levels (<3.7 μg/dL) were exposed to 22 μg/wipe and 380 μg/g, respectively. In addition, 79% of the homes of the children with high blood lead levels had been refinished while only 56% of the homes had been refinished among the children with low blood lead levels, suggesting that refinishing the interior of homes with leaded paint may increase, at least temporarily, a child's exposure to lead dust (Rabinowitz et al. 1985). Blood lead levels in children have been found to increase during the summer months when children play outdoors and soil dust is more common. After interior and exterior lead dust cleanup procedures were instituted around areas known to have high soil lead levels, the blood lead concentrations dropped in 52% of the children (Mielke et al. 1992).

Secondary occupational exposure may occur among families of workers who inadvertently bring home lead dusts on clothing worn at work. Blood lead levels of children in households of occupationally exposed workers were almost twice those of children in neighboring homes whose parents were not occupationally exposed to lead, median range of 10–14 μg/dL and 5–8 μg/dL, respectively (Grandjean and Bach 1986).

Another source of dietary lead is the use of inadequately glazed earthenware vessels used for food storage and cooking. Due to the number of incidences of lead poisoning that have resulted from the use of earthenware vessels, the FDA has established action levels of 0.5 μg/mL lead for pitchers to 5.0 μg/mL for cups and mugs soaked for 24 hours in a 4% acetic acid solution (FDA 1992a). However, inadequately glazed pottery manufactured in other countries continues to pose a significant health hazard. Likewise, homemade or craft pottery and porcelain-glazed vessels have been found to release large quantities of lead, particularly if the glaze is chipped, cracked, or improperly applied. In addition, glaze on vessels that are washed repeatedly may deteriorate, and a vessel that previously met FDA standards may become unsafe (CDC 1985; EPA 1986a).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to the workers that are exposed to lead in the workplace, several other groups of populations at risk for potential exposure to high levels of lead can be identified: preschool-age children, fetuses, populations living near NPL sites, and white males between 40 and 59 years of age (EPA 1986d).

Young children are potentially exposed to lead because of their tendency to ingest soils that may be contaminated with lead. It has been estimated that children may ingest between 20 and 50 mg of soil per day. If the soil contains 100 μg/g of lead, a child may be exposed to 25 μg of lead per day by this alone (Mielke et al. 1989). Fetuses are at even greater risk. As discussed in Section 2.7 on populations that are unusually susceptible, lead can readily cross the placenta; therefore, exposure of women to lead during pregnancy results in uptake by the fetus. Furthermore, since the physiological stress of pregnancy may result in mobilization of lead from maternal bone, fetal uptake of lead can occur from a mother who was exposed to lead before pregnancy, even if no lead exposure occurs during pregnancy. Prenatal exposure may be related to postnatal mental retardation, impaired postnatal neurobehavioral development, and reduced birth weight and gestational age (EPA 1986a).

General population exposure is most likely to occur through the ingestion of food and water that are contaminated with lead, however, some individuals and families may be exposed to additional sources of lead in their homes. This is particularly true of older homes that may contain lead-based paint. In an attempt to reduce the amount of exposure due to deteriorating leaded paint, the paint is commonly removed from homes by burning (gas torch or hot air gun), scraping, or sanding. These activities have been found to result, at least temporarily, in higher levels of exposure for families residing in these homes. In addition, those individuals involved in the paint removal process (i.e., do-it-yourself renovators and professionals who remove lead) can be exposed to such excessive levels that lead poisoning may occur (Chisolm 1986; Feldman 1978; Fischbein et al. 1981; Rabinowitz et al. 1985). Improper removal of lead from housing known to contain lead-based paint can significantly increase lead levels in dust, thus causing lead toxicity in children living in the home during the lead removal process; four such cases have been documented (Amitai et al. 1987).

Young children (less than 6 years old) of workers exposed to high levels of lead in workplace air at an electronic components plant (61–1,700 μg lead/m^3 ambient concentrations) had significantly elevated blood lead levels (13.4 μg/dL) when compared with children from the same locale whose parents did not work in the electronics plant (7.1 μg/dL), although none of the children had blood lead levels in excess of the lead toxicity guideline of 10 μg/dL (CDC 1991).

Increased blood pressure is associated with blood lead concentrations possibly as low as 7 μg/dL. It appears that this relationship is particularly significant for middle-aged white males (aged 40–59) (EPA 1986a).

Populations living near the 922 NPL sites that were identified as having lead present in the environmental media may be at risk for exposure to high levels of lead. However, the available data are insufficient to allow characterization of the sizes of these populations or intake levels of lead to which they may be exposed.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of lead is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of lead.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of lead and its compounds are sufficiently well defined to allow an estimation of the environmental fate of lead to be made (Budavari et al. 1989; Howe 1981; HSDB 1990, 1992; Lide 1992; Sax 1984; Sax and Lewis 1987). Availabilities of the various forms need to be modeled.

Production, Import/Export, Use, and Release and Disposal. Lead is produced and imported for widespread use in the United States. Therefore, the potential for human exposure in the workplace, the home, the environment, and at waste sites may be substantial.

Lead is produced from both primary (i.e., mined ore) and secondary (i.e., scrap metal and wastes) sources, and is imported by the United States. In 1990, production from primary and secondary sources was 878 million pounds and 923 thousand pounds, respectively (U.S. Department of the Interior 1991), and imports reached 93,000 metric tons (U.S. Department of Commerce). U.S. consumption of lead was approximately 1,473 million pounds during that year (U.S. Department of Commerce 1992). In 1986, 70% of the lead consumed went for lead acid batteries, gasoline additives, and other applications. Construction, ammunition, electrical uses, television glass, and paint represented 25% of consumption and 5% was used for ceramics, type metal, ballast or weights, tubes or containers (U.S. Department of Interior 1987b). Because of the adverse health effects associated with exposure to lead, its use in paints, ceramic products, gasoline additives, and solder has declined in recent years. Between 1981 and 1989, lead exports fluctuated between 4,000 metric tons and 51,000 metric tons before reaching a level only 19,000 metric tons below the level of imports in 1990 (U.S. Department of Commerce 1992). As a result of the decline in the use of lead in gasoline, updated information on the release and disposal of lead would be helpful in assessing accurately the potential for exposure to lead and its compounds.

Lead is recycled or disposed in landfills. An estimated 70–75% of the lead consumed in the United States can be recycled. In 1981, approximately 50% of the demand for lead was met through recycling lead products, mostly lead batteries (Howe 1981). Industrial wastes as well as consumer products containing lead are disposed of in municipal and hazardous waste landfills. Current information on the amounts being recycled and disposed is needed to evaluate the potential for exposure to lead.

The federal government regulates the release and disposal of lead. EPA has established national ambient air quality standards for lead. Under the Safe Drinking Water Act, EPA limits the level of lead in drinking water. Industrial emissions are regulated by the Clean Water Act. Lead and certain of its compounds are designated hazardous substances; CERCLA requires that the person in charge of a vessel or facility notify the National Response Center immediately when there is a release of a hazardous substance in an amount equal to or greater than the reportable quantity for that substance.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory, which contains this information for 1988, became available in May of 1990 (TRI88 1990). This database is updated yearly and provides a list of industrial production facilities and emissions.

Environmental Fate. Lead released to the atmosphere partitions to surface water, soil, and sediment (Getz et al. 1977; EPA 1986a; Mundell et al. 1989; NAS 1980; NSF 1977; Nielsen 1984). Lead is transported in the atmosphere and in surface water. Organolead compounds are transformed in the atmosphere by photodegradation (DeJonghe and Adams 1986); however, the atmospheric transformation of inorganic lead compounds is not completely understood (EPA 1986a). Organolead compounds are transformed in surface waters by hydrolysis and photolysis (EPA 1979d). Inorganic lead compounds may be strongly sorbed to organic matter in soils and sediments (EPA 1986a). Lead is a naturally occurring element and as such is persistent in the environment. Additional information on the atmospheric transformations of organic and inorganic lead compounds in the atmosphere would provide a basis for determining the lead compounds to which humans are most likely to be exposed. Modeling the availability of lead compounds needs to be accomplished.

Bioavailability from Environmental Media. Available pharmacokinetic data indicate that lead is absorbed by humans following inhalation of particulate lead in ambient air and ingestion of contaminated foods, drinking water, and soil (Chamberlain et al. 1978; EPA 1986a; Morrow et al. 1980). In addition, children may ingest paint chips that contain lead. Absorption following dermal exposure is much more limited, although absorption of organolead compounds through the skin has been reported following accidental exposures (Kehoe and Thamann 1931; Laug and Kunze 1948; Moore et al., 1980). The bioavailability of lead on the hand after mouthing activity needs to be modeled.

Food Chain Bioaccumulation. Lead is bioaccumulated by terrestrial and aquatic plants and animals (Eisler 1988). However, lead is not biomagnified in terrestrial or aquatic food chains (Eisler 1988). No additional information is needed.

Exposure Levels in Environmental Media. Environmental monitoring data are available for lead in ambient air, indoor air, surface water, groundwater, drinking water, sediments, soils, and foodstuffs (Eckel and Jacob 1988; EPA 1982a, 1986a, 1988b, 1988f, 1989f, 1989h, 1990c; Lee et al. 1989; Maenhaut et al. 1979; Mielke 1992; Mielke et al. 1983, 1985, 1989); however, these data are not current and additional monitoring data on lead levels in all environmental media, particularly data gathered after EPA lowered the lead content of gasoline, would be helpful in determining current exposure levels. Estimates of human intake from inhalation of ambient air and ingestion of contaminated foods and drinking water are available (Dabeka et al. 1987; EPA 1986a, 1991d; Gartrell et al. 1986b; Gunderson 1988). Estimates are also available for intake by children through ingestion of contaminated soils, dust, and paint chips (EPA 1989c). However, some of these estimates also are not current. Additional information on the concentrations of lead compounds in environmental media, particularly at hazardous waste sites, and an estimate of human intake would be helpful in establishing human exposure lead.

Exposure Levels in Humans. Lead can be measured in human blood, hair, perspiration, teeth, bones, feces, and urine (Aguilera et al. 1989; Batuman et al. 1989; Blakley and Archer 1982; Blakley et al. 1982; Christoffersson et al. 1986; Delves and Campbell 1988; Ellen and Van Loon 1990; Exon et al. 1979; Hu et al. 1989, 1990, 1991; Jason and Kellogg 1981; Manton and Cook 1984; NIOSH 1977a, 1977d, 1977e, 1977f, 1977g 1977h; Que Hee and Boyle 1988; Que Hee et al. 1985a; Wielopolski et al. 1986). The most common method of assessing human exposure involves measurement of lead in blood (Aguilera et al. 1989; Delves and Campbell 1988; Manton and Cook 1984; NIOSH 1977a, 1977d, 1977e, 1977f, 1977g 1977h; Que Hee et al. 1985a). Blood lead levels have been correlated with ambient air exposure levels and dust, and dietary intake levels (Rabinowitz et al. 1985). Additional information on the biological monitoring of populations living in the vicinity of hazardous waste sites would be helpful in estimating exposure of these populations to lead compounds. The relationships between the major biological monitoring media should be determined. Alkyl lead compounds can be measured in exhaled breath.

Exposure Registries. No exposure registries for lead were located. This substance is not currently one of the substances for which a subregistry has been established in the National Exposure Registry. The substances will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this substance.

5.7.2 On-going Studies

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, will be analyzing human blood samples for lead. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring lead in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify lead. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect lead in environmental samples are the methods approved by federal organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

Blood, Urine, Serum, Cerebrospinal Fluid. There are several methods for the analysis of lead in biological samples. The most common methods currently used are flame atomic absorption spectrometry (AAS), graphite furnace atomic absorption spectrometry (GFAAS), anode stripping voltammetry (ASV), and inductively coupled plasma-atomic emission spectroscopy (ICP-AES). Spectrophotometric methods also exist and were commonly used in the past; however, they are not as sensitive or reliable as the newer methods. According to Grandjean and Olsen (1984), GFAAS and ASV are the methods of choice for the analysis of lead. In order to produce reliable results, background correction must be applied. Other specialized methods for lead analysis are inductively coupled plasma-mass spectrometry (ICP-MS), X-ray fluorescence spectroscopy (XRFS), neutron activation analysis (NAA), differential pulse anode stripping voltammetry, and isotope dilution mass spectrometry (IDMS). The most reliable method for the determination of lead at low concentrations is IDMS (EPA 1986a; Grandjean and Olsen 1984), but due to the technical expertise required and high cost of the equipment, this method is not commonly used. It is primarily used for the development of certified standard reference materials by which other methods can determine their reliability since results of lead analyses from numerous laboratories often do not agree (Fell 1984). Details of several methods used for the analysis of lead in biological samples are presented in Table 6-1.

Concentrations of lead in blood, urine, serum, and cerebrospinal fluid have been used as indicators of exposure to lead. Measurement of lead in blood is the most common method of assessing exposure. Sample preparation usually consists of wet ashing the sample with strong acid and heat, and redissolving the residue in dilute acid prior to analysis so that all lead species are converted quantitatively to the same lead compound (NIOSH 1977a, 1977d, 1977e, 1977g, 1977h). Preparation methods not requiring wet ashing have also been used with good results (Aguilera et al. 1989; Delves and Campbell 1988; Manton and Cook 1984; NIOSH 1977f; Que Hee et al. 1985a). For samples analyzed by ICP-MS, ASV, AAS, and GFAAS, sensitivity is in the low- to sub-ppb (2.4–15 ppb) with good accuracy and precision (Aguilera et al. 1989; Delves and Campbell 1988; NIOSH 1977d, 1977e, 1977f, 1977g, 1977h; Que Hee et al. 1985a). A comparison of IDMS, ASV, and GFAAS showed that all three of these methods can be used to reliably quantify lead levels in blood (Que Hee et al. 1985a). ACGIH recommends quantification of blood lead by the GFAAS. For analysis of urine, chelation and solvent extraction, followed by atomic absorption for quantification is the recommended method (ACGIH 1986). Estimated accuracy reported for an IDMS technique was excellent (Manton and Cook 1984). Sensitivity and precision were not reported by the authors, but they are generally considered to be excellent (EPA 1986a; Grandjean and Olsen 1984).

TABLE 6-1. Analytical Methods for Determining Lead in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Sample wet ashed with acid mixtures; residue dissolved in dilute $HClO_4$	ASV with mercury-graphite electrode (NIOSH method P&CAM 195)	40 μg/L	95–105	NIOSH 1977d
Blood	Sample wet ashed with HNO_3; residue dissolved in dilute HNO_3	GFAAS (NIOSH method P&CAM 214)	100 μg/L	NR	NIOSH 1977g
Blood	Sample diluted with Triton X-100®; nitric acid and diammonium phospate added	GFAAS	2.4 μg/L	93–105	Aguilera et al. 1989
Blood	Dilute sample with ammonium solution containing Triton X-100; analyze	ICP-MS	15 μg/L	96–111	Delves and Campbell 1988
Blood	Dilute sample in 0.2% Triton X-100 and water; analyze	GFAAS	~15 μg/L	97–150	Que Hee et al. 1985a
Blood and urine	Urine sample mixed with HNO_3; filtered, whole blood or filtered urine chelated with APDC, and extracted with MIBK	AAS (Method P&CAM 8003)	0.05 μg/g (blood) or 10 μg/mL (urine)	99	NIOSH 1984
Blood and urine	Sample wet ashed with HNO_3, complexed with diphenylthiocarbazone, and extracted with chloroform	Spectrophotometry (NIOSH method P&CAM 102)	30 μg/L (blood); 12 μg/L (urine)	97 97	NIOSH 1977a

TABLE 6-1 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood and urine	^{206}Pb added and sample acid digested; lead coprecipitated by addition of $Ba(NO_3)_2$, followed by electrodeposition on platinum wire	IDMS	NR	98–99	Manton and Cook 1984
Blood and tissue	Digest sample with $HNO_3/HClO_4/H_2SO_4$; heat	ICP-AES (Method P&CAM 8005)	0.01 μg/g (blood) 0.2 μg/g (tissue)	113	NIOSH 1985a
Urine	Extract sample with polydithiocarbamate resine and NaOH; filter on cellulose ester membrane; neutralize with NaOH; ash; dissolve and heat; dilute with distilled water	ICP-AES (Method P&CAM 8310)	0.005 μg/mL	100	NIOSH 1984
Serum blood, and urine	Filter sample if needed; blood requires digestion in a Paar bomb; dilute serum or urine with acid or water	ICP-AES	10-50 μg/L	85 (serum) >80 (urine, blood)	Que Hee and Boyle 1988
Urine	Sample wet ashed with acid mixture and dissolved in dilute $HClO_4$	ASV with mercury-graphite electrode (Method P&CAM 200)	4 μg/L	90–110	NIOSH 1977e

TABLE 6-1 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine (δ-aminolevulinic acid)	Dilute sample; react with ethylacetoacetate and ethylacetate to form δ-aminolevulinic acid-pyrrole; react with Erhlich's reagent	Spectrophotometry	NR	NR	Tomokuni and Ichiba 1988
Urine (δ-aminolevulinic acid)	Acidify sample; separate δ-aminolevulinic acid on HPLC; react with formaldehyde and acetylacetone	HPLC/FL	10 μg/L	NR	Tabuchi et al. 1989
Serum and cerebrospinal fluid	^{206}Pb added and sample acid digested; lead separated by ion-exchange, eluted, and deposited onto platinum wire	IDMS	NR	80–120	Manton and Cook 1984
Feces	Dry and pulverize sample; digest with hot acid in Paar bomb	ICP-AES	10-50 μg/L	>86	Que Hee and Boyle 1988
Testes, liver, spleen, kidney	Dice sample and digest in hot acid in a Paar bomb; evaporate; redissolve in HCl/HNO_3	ICP-AES	10-50 μg/L	>80	Que Hee and Boyle 1988
Spleen, liver, and kidney	Sample wet digested with HNO_3-$HClO_4$ mixture	GFAAS	NR	NR	Blakley and Archer 1982; Blakley et al. 1982

TABLE 6-1 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Liver, kidney, muscle	Bomb digest sample with acid and heat or digest with acid and dry ash; dissolve in acid; dilute with water	GFAAS	20 μg/g (bomb); 5 μg/g (dry ashing)	85–107 (bomb); 75–107 (dry ashing)	Ellen and Van Loon 1990
		DPASV	NR	82–120	
Tissues (brain, heart, lung, kidney, liver, and testes)	Sample dry ashed; dissolved in HNO_3	AAS	NR	NR	Exon et al. 1979
Tissues	Freeze dry samples; subject to thermal neutron irradiation; chemically separate elements	NAA	NR	NR	Hewitt 1988
Brain	Sample wet ashed with mixture of acids, mixed with Metex® and analyzed	ASV	NR	NR	Jason and Kellogg 1981
Bone	Partially polarized photon directed at second phalanx of left forefinger (non-invasive technique)	K-XRF	20 μg/g	NR	Christoffersson et al. 1986
Bone	Partially polarized photon directed at anteromedial skin surface of mid-tibia (non-invasive technique)	L-XRF	20 μg/g	NR	Wielopolski et al. 1986

TABLE 6-1 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Teeth	Clean and section tooth; digest with HNO_3; evaporate; redissolve in buffer solution	ASV	NR	83–114	Rabinowitz et al. 1989
Teeth	Sample dry ashed; crushed; dry ashed again; dissolved in HNO_3	AAS	NR	90–110	Steenhout and Pourtois 1981
Hair	Sample cleaned with acetone/ methanol; digested with acid mixture and heat; diammonium phosphate added as matrix modifier	GFAAS	0.16 μg/g	99	Wilhelm et al. 1989
Bone	^{109}Cd gamma-ray source at 2.5 cm from skin of proximal tibia	K-XRF	2 μg/g	NR	Hu et al. 1989, 1990, 1991
Hair	Sample cleaned with hexane, ethanol, and water; wet ashed with HNO_3 and H_2O_2	ICP-AES	NR	NR	Thatcher et al. 1982

AAS = atomic absorption spectrometry; APDC = ammonium pyrrolidine dithiocarbamate; ASV = anode stripping voltammetry; $Ba(NO_3)_2$ = barium nitrate; ^{109}CD = cadmium 109 radioisotope; DPASV = differential pulse anodic stripping voltammetry; GFAAS = graphite furnace atomic absorption spectrometry; H_2O_2 = hydrogen peroxide; HCl = hydrogen chloride; H_2SO_4 = sulfuric acid; $HClO_4$ = perchloric acid; HNO_3 = nitric acid; HPLC/FL = high performance liquid chromatography/fluorimetry; ICP-AES = inductively coupled plasma-atomic emission spectroscopy; ICP-MS = inductively coupled plasma-mass spectrometry; IDMS = isotope dilution mass spectrometry; K-XRF = K-wave x-ray fluorescence; L-XRF = L-wave x-ray fluorescence; MIBK = methyl isobutyl ketone; NAA = neutron activation analysis; NaOH = sodium hydroxide; NIOSH = National Institute for Occupational Safety and Health; NR = not reported; P&CAM = physical and chemical analytical methods; ^{206}Pb = lead 206

Several biomarkers exist for monitoring exposure to lead. A number of biochemical assays are available for the assessment of lead exposure and toxicity in the human body using standard clinical laboratory techniques. Details of such assays are reported in several reviews (EPA 1986a; Grandjean and Olsen 1984; Stokinger 1981) and are also available in standard clinical laboratory methods manuals. The commonly used assays are coproporphyrin, 1,25-dihydroxyvitamin D, ALA, and EP concentrations and ALAD activity. All of these assays are sensitive, reliable, and well established; however, erythrocyte protoporphyrin and ALAD activity appear to be the most useful and sensitive for determining exposure to lead. A colorimetric method for detection of ALA in urine, in which the pyrrole from ALA is formed and reacted with Ehrlich's reagent to form a colored end product, has been used successfully (Tomokuni and Ichiba 1988). ALA has also been extracted from urine using high-performance liquid chromatography (HPLC) followed by quantification of a fluorescent end product (Tabuchi et al. 1989). Data provided on the methods were insufficient to adequately evaluate or compare their sensitivity and reliability. Erythrocyte protoporphyrin bound to zinc has been quantified using hemofluorimetry (Braithwaite and Brown 1987). An HPLC/fluorescent method has been reported for determination of coproporphyrin in urine (Tomokuni et al. 1988). Other biological assays that have been used as indicators of lead exposure are serum immunoglobulins and salivary IgA (Ewers et al. 1982). While all these biological assays are reliable and have been verified for clinical laboratory use, they are not specific for lead.

Tissues. Lead has been quantified in a variety of tissues, including liver, kidney, brain, heart, lung, muscle, and testes. Techniques for measuring lead in tissues are similar to those used for blood and urine. When AAS, GFAAS, or ASV are used for analysis, the samples may be wet ashed, digested with acid, or bomb digested (Blakley and Archer 1982; Blakley et al. 1982; Ellen and Van Loon 1990; Exon et al. 1979; Jason and Kellogg 1981; Que Hee and Boyle 1988). The information located did not allow an adequate comparison between these methods. Parr bomb digestions are recommended for estimation of metals in biological tissues (Que Hee and Boyle 1988). Sensitivities reported for GFAAS and ICP-AES are in the low ppm (5-20 ppm) (Ellen and Van Loon 1990) and are probably comparable for the other techniques. Differential anodic stripping pulse voltammetry (DPASV) and NAA have also been used to analyze tissues for lead. Sample preparation for DPASV is the same as those for AAS, GFAAS, and ASV. Its accuracy and precision are comparable to results using GFAAS, and its sensitivity is slightly greater (Ellen and Van Loon 1990). Determination of lead in tissue samples following freeze drying, neutron irradiation, and chemical separation has been reported. An advantage of this method is that the sample does not have to be dissolved. No further information was reported for the method (Hewitt 1988).

Hair, Teeth, and Bone. Noninvasive methods using X-ray fluorescence can be used for the determination of lead concentration in bones. These methods include L X-rays of the tibia using an X-ray generator (Wielopolski et al. 1986); K X-rays in the second phalanx of the index finger using a cobalt source and a germanium silicon detector (Christoffersson et al. 1986); and in vivo tibial K X-ray fluorescence (Batuman et al. 1989; Hu et al. 1989, 1990, 1991). This latter method has the advantage of deeper penetration of the bone (2 cm) to allow for averaging lead concentrations over the whole bone thickness (Wedeen 1990). The level of lead in bone has been reported to be a good indicator of stored lead in body tissue (Ahlgren et al. 1976; Bloch et al. 1976; Rosen et al. 1987). The sensitivity of the technique is in the low ppm and the precision is acceptable. Advantages are that no sample preparation is required and the technique can safely and easily be done on live subjects. Teeth have been analyzed for lead using AAS and ASV (Rabinowitz et al. 1989; Steenhout and Pourtois 1981). Samples must be dry ashed or digested with acid prior to analysis. Precision and accuracy of both AAS and ASV are good. Detection limits were not reported by the authors. A detection limit in the sub-ppm (0.16 ppm) and high accuracy were reported for GFAAS analysis of hair samples (Wilhelm et al. 1989). ICP-AES has also been used to analyze hair for lead, but lack of data prevents a comparison with the AAS method (Thatcher et al. 1982).

6.2 ENVIRONMENTAL SAMPLES

The primary methods of analyzing for lead in environmental samples are AAS, GFAAS, ASV, ICP-AES, and XRFS. Less commonly employed techniques include gas chromatography/photoionization detector (GC/PID), IDMS, DPASV, electron probe X-ray microanalysis (EPXMA), and laser microprobe mass analysis (LAMMA). In determining the lead concentrations in the atmosphere and water, a distinction between the concentration of lead in the particulate and gaseous or dissolved forms is often necessary. Particulate lead can be separated from either media using a filter technique. The filter collects the particulate matter and allows the dissolved material to pass through for separate analysis of each form. As with the analysis of biological samples, the definitive method of analysis for lead is IDMS. However, most laboratories do not possess the expertise or equipment required for this method. Table 6-2 summarizes several methods for determining lead in a variety of environmental matrices.

Air. A variety of methods have been used to analyze for particulate lead in air. The primary methods, AAS, GFAAS, ICP-AES are sensitive to levels in the low $\mu g/m^3$ range (0.1–20 $\mu g/m^{3)}$ (Birch et al. 1980; EPA 1988b; NIOSH 1977c, 1977g, 1981, 1984; Scott et al. 1976). Accuracy and precision are generally good. GFAAS is considered to be more sensitive than AAS; however, AAS is not subject to as much interference from matrix effects as GFAAS (NIOSH 1977b, 1977g, 1977i). Detection of particulate lead by generation of the lead hydride has been used to increase the sensitivity of the AAS technique (Nerin et al. 1989). Excellent accuracy and precision was reported for this method. ASV has a wide range as well as high sensitivity. It is relatively inexpensive compared to other methods (NIOSH 1977b). Advantages of ICP-AES are that it has a wide range and allows analysis of several elements at once. However, the technique is expensive in terms of equipment and supplies (NIOSH 1981). XRFS has been used to analyze for particulate lead in air (DeJonghe et al. 1981). While sensitivity was good, recovery was highly variable and relatively low compared to other methods. The highest sensitivity was obtained with IDMS, as expected (Volkening et al. 1988). As previously stated, this is the definitive method for determining lead in environmental, as well as biological samples. Two sophisticated methods, EPXMA and LAMMA, have been used to determine the inorganic lead species present in particulate matter in air (Van Borm et al. 1990).

Determination of lead vapor in air requires prior filtering of the air to exclude particulate lead, and trapping of the gaseous components. Gaseous lead is also referred to as organic lead or alkyl lead, the most common being the tetraalkyl species. Organic lead species may be trapped by liquid or solid sorbents, or cryogenically (Birch et al. 1980; DeJonghe et al. 1981; NIOSH 1978b). Gas chromatography (GC) is used to separate the different alkyl species. Detection by GFAAS and PID have been reported (DeJonghe et al. 1981; NIOSH 1978b). GFAAS detection is more sensitive than PID, but both have good accuracy.

Water. As with air, water can be analyzed for both particulate and dissolved (organic) lead. Particulate lead collected on a filter is usually wet ashed prior to analysis. Comparison of the GFAAS and AAS methods for particulate lead showed the former technique to be about 100 times more sensitive than the latter, although both offer relatively good accuracy and precision (EPA 1983). GC/AAS has been used to determine organic lead, present as various alkyl lead species, in water (Chakraborti et al. 1984; Chau et al. 1979, 1980). Sample preparation for organic lead analysis was either by organic solvent extraction (Chakraborti et al. 1984; Chau et al. 1979) or purge-and-trap (Chau et al. 1980). Sensitivity was in the ppb to ppt range and reliability was similar for all three methods. Total lead can be determined by

TABLE 6-2. Analytical Methods for Determining Lead in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (particulate lead)	Particulate matter collected on membrane filter; wet ashed with HNO_3; diluted with distilled water	GFAAS (Method P&CAM 7105)	0.2 $\mu g/m^3$	82–103	NIOSH 1990
Air (particulate lead)	Particulate matter collected on membrane filter; wet ashed with $HNO_3/HClO_4/H_2SO_4$; dissolved in acetate buffer	ASV with mercury-graphite electrode (Method P&CAM 191)	0.16 $\mu g/m^3$	90–110	NIOSH 1977c
Air (particulate lead)	Particulate matter collected on membrane filter; wet ashed with HNO_3; aspirated into AA unit	AAS flame (Method 7082)	25 $\mu g/m^3$	82–103	NIOSH 1984
Air (particulate lead)	Particulate matter collected on cellulose acetate membrane filter; wet ashed with $HNO_3/HClO_4$	ICP-AES (Method P&CAM 7300)	5 $\mu g/m^3$	95–105	NIOSH 1984
Air (particulate lead)	Particulate matter collected on filter; extracted with HNO_3/HCl, heat, and sonication	ICP-AES	NR	NR	EPA 1988a
Air (particulate lead)	Particulate matter collected on filter; dry ashed; extracted with HNO_3/HCl; diluted with HNO_3	AAS AES	0.1 $\mu g/m^3$ 0.15 $\mu g/m^3$	93 102	Scott et al. 1976

TABLE 6-2 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (particulate lead)	Collect sample on cellulose acetate filter; dissolve in HNO_3 with heat; add HCl/H_2O_2 and react in hydride generator with sodium borohydride to generate lead hydride	AAS	8 ng/L	100–101	Nerin et al. 1989
Air (particulate lead)	Collect sample on filter; spike filter with ^{206}Pb; dissolve filter in NaOH; acidify; separate lead by electrodeposition; dissolve in acid	IDMS	0.1 ng/m^3	NR	Volkening et al. 1988
Air (particulate lead)	Collect sample on nucleopore polycarbonate filter; coat filter sections with carbon	EPXMA LAMMA	NR NR	NR NR	Van Borm et al. 1990
Air (gaseous lead)	Filtered sample adsorbed on XAD-2 resin, desorbed with pentane	GC/PID (Method 2534 (TML) and 2537 (TEL))	40 $\mu g/m^3$ (TML) 45 μg/m3 (TEL)	99 105.5	NIOSH 1987
Air (particulate and organolead)	Particulate matter collected on glass fiber filter; filtered gases passed through iodine monochloride bubblers; particulate matter wet ashed; bubbler solution converted to dithiazone complex in presence of EDTA-salts and extracted with carbon tetrachloride solution followed by acid extraction	GFAAS	NR (particulate); 0.25 ng/m^3 (gaseous)	NR (particulate); 95–99 (gaseous)	Birch et al. 1980

TABLE 6-2 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (particulate and organolead)	Particulate matter collected on nucleopore filters; filtered gases cryogenically trapped and thermally desorbed	XRF (particulate) GC/GFAAS (gaseous)	0.3 $\mu g/m^3$ 0.2 ng/m^3	46->90 90–100	DeJonghe et al. 1981
Water (particulate and dissolved lead)	Filtered through a 0.45-μm membrane filter (dissolved lead); filtered material dissolved by wet ashing (insoluble lead)	ICP-AES (EPA method 200.7)	42 $\mu g/L$	94–125	EPA 1983
Water (TAL)	Sample extracted with hexane	GC/AAS	0.5 $\mu g/L$	88–90	Chau et al. 1979
Water (TAL)	Purge sample; cryogenically trap on solid sorbent GC column	GC/AAS	0.5 ng/g	NR	Chau et al. 1980
Water (alkyl lead)	Sample complexed with diethyldithiocarbamate; extracted with pentane; dried; butylated; extracted with nonane	GC/AAS	1.25 ng/L	90–108	Chakraborti et al. 1984
Water (particulate and dissolved lead)	Filtered through a 0.45-μm membrane filter (dissolved lead); filtered material dissolved by wet ashing (insoluble lead)	AAS (EPA Method 239.1) GFAAS (EPA Method 239.2)	0.1 mg/L 1 $\mu g/L$	99.8–125.7 88–95	EPA 1983
Water (total lead)	Digest sample with acid; heat; dilute with water	AAS	1.0 ng/g	NR	Chau et al. 1979

TABLE 6-2 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water (total lead)	Filter sample; analyze; heat or dilute with acid	ICP-AES	10-50 μg/L	>80	Que Hee and Boyle 1988
Soil	Dry sample and sieve; digest with HNO_3; centrifuge	ICP-AES	0.09 μg/g	97–103	Schmitt et al. 1988
Soil	Dry sample and sieve for XRF; digest sieved sample with HNO_3 and heat for AAS	XRF AAS	NR NR	65–98 63–68	Krueger and Duguay 1989
Soil	Sample dried, dry ashed, digested with acid, and diluted with water	AAS	2 μg/g	79–103	Beyer and Cromartie 1987
Soil, wastes, and groundwater	Sample acid digested, diluted with water, and filtered	AAS (EPA method 7420) GFAAS (EPA method 7421)	0.1 mg/L 1 μg/L	NR NR	EPA 1986e
Soil, dust, and paint	Digest sample with hot acid; dry; redissolve in HNO_3	AAS	12 ng/g	>80	Que Hee et al. 1985b
Sediment	Hot digest sample with HNO_3/H_2SO_4	GFAAS	NR	92–95	Bloom and Crecelius 1987
Sediment, fish (TAL)	Homogenize fish; add EDTA to sample; extract with hexane; centrifuge; analyze organic layer	GC/AAS	0.01 μg/g (sediment) 0.025 μg/g (fish)	81–85 72–76	Chau et al. 1979

TABLE 6-2 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Sediment, fish, vegetation (TAL)	Purge sample; cryogenically trap on solid sorbent GC column	GC/AAS	0.1 ng/g (solid)	NR	Chau et al. 1980
Sediment, fish, vegetation (total lead)	Digest sample with acid; heat; dilute with water	AAS	50 ng/g (sediment)	NR	Chau et al. 1980
			10 ng/g (fish and vegetation)	NR	
Milk	50 μL $(C_2H_5)_4NOH$ in ethanol added to 25 μL mild, heated, and diluted with water to 125 μL	GFAAS	NR	NR	Michaelson and Sauerhoff 1974
Evaporated milk	Dry ash sample; dissolve in HNO_3	ASV	0.005 μg/g	99	Capar and Rigsby 1989
Mussel, tomato	Wet ash sample with acid or acid plus catalyst; generate lead hydride	GFAAS	4 ng/g	94–95	Aroza et al. 1989
Agricultural crops	Sample dry ashed with H_2SO_4 and HNO_3; diluted with water	DPASV	0.4 ng/g	85–106	Satzger et al. 1982
Grains, milk mussel, fish	Bomb digest sample with acid and heat or digest with acid and dry ash; dissolve in acid; dilute with water	GFAAS	20 μg/g (bomb);	85–107	Ellen and Van Loon 1990
			5 μg/g (dry ash)	75–107	
		DPASV	NR	82–120	

TABLE 6-2 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Citrus leaves and paint	Chop or pulvarize sample; digest with hot acid; dry; redissolve in acid	ICP-AES	10–50 μg/L	75–82 (citrus leaves); 89–96 (paint)	Que Hee and Boyle 1988

AA = atomic absorption; AAS = atomic absorption spectroscopy; AES = atomic emissions spectroscopy; ASV = anode stripping voltammetry; $(C_2H_5)_4NOH$ = tetraethylammonium hydroxide; DPASV = differential pulse anodic stripping voltammetry; EDTA = ethylenediamine tetraacetic acid; EPA = Environmental Protection Agency; EPXMA = electron probe x-ray micro-analysis; GC = gas chromatography; GFAAS = graphite furnace atomic absorption spectrometry; HCl = hydrochloric acid; $HClO_4$ = perchloric acid; HNO_3 = nitric acid; H_2O_2 = hydrogen peroxide; H_2SO_4 = sulfuric acid; ICP-AES = inductively coupled plasma-atomic emission spectroscopy; IDMS = isotope dilution mass spectrometry; LAMMA = laser microprobe mass analysis; MS = mass spectrometry; NaOH = sodium hydroxide; NG = nanogram; NR = not reported; ^{206}Pb = lead 206; P&CAM = physical and chemical analytical methods; PID = photoionization detector; TAL = tetraalkyl leads; TEL = tetraethyl lead; TML = tetramethyl lead; XRF = X-ray fluorescence digesting samples with acid and analyzing by either AAS or the more sensitive GFAAS (Chau et al. 1980; EPA 1982c, 1986e).

Dusts, Sediments, and Soil. Both total and organic lead have been determined in dusts, sediments, and soils. In most cases the sample must be digested with acid to break down the organic matrix prior to analysis (Beyer and Cromartie 1987; Bloom and Crecelius 1987; EPA 1982c, 1986e; Krueger and Duguay 1989; Que Hee and Boyle 1988; Que Hee et al. 1985b; Schmitt et al. 1988), although organic extraction (Chau et al. 1979) and purge-and-trap (Chau et al. 1980) have been used. The primary detection methods are AAS or GFAAS with GFAAS more sensitive, but also more susceptible to interference. When quantification of organic lead is desired, GC is employed to separate the alkyl lead species (Chau et al. 1979,1980). Precision and accuracy are acceptable for these atomic absorption-based methods (Beyer and Cromartie 1987; Bloom and Crecelius 1987; Chau et al. 1979; EPA 1982c, 1986e; Krueger and Duguay 1989; Que Hee et al. 1985b). ICP-AES is reported to be more sensitive and reliable than atomic absorption techniques (Schmitt et al. 1988), but sample collection and preparation methods have been shown to strongly influence the reliability of the overall method (Que Hee et al. 1985b). Sampling of house dust and hand dust of children requires special procedures (Que Hee et al. 1985b). XRFS appears to provide a simpler method of measuring lead in soil matrices; however, the available data do not permit an assessment of the techniques sensitivity and reliability for soil analysis (Krueger and Duguay 1989).

Other Matrices. Lead has been determined in several other environmental matrices, including paint, fish, vegetation, agricultural crops, and various foods. As with soil, the methods of choice are either ICP-AES, AAS, or GFAAS. Samples may be prepared using one of the methods described for sediment and soil or by wet or dry ashing (Aroza et al. 1989; Capar and Rigsby 1989; Que Hee and Boyle 1988; Que Hee et al. 1985b; Satzger et al. 1982). ASV and DPASV have also been used with good sensitivity (ppb) and reliability to analyze for lead in other environmental media (Capar and Rigsby 1989; Ellen and Van Loon 1990; Satzger et al. 1982).

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of lead is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of lead.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Methods are available for measuring inorganic lead in blood, serum, urine, cerebrospinal fluid, tissues, bone, teeth, and hair (Aguilera et al. 1989; Batuman et al. 1989; Blakley and Archer 1982; Blakley et al. 1982; Christoffersson et al. 1986; Delves and Campbell 1988; Ellen and Van Loon 1990; Exon et al. 1979; Hu et al. 1989, 1990, 1991; Jason and Kellogg 1981; Manton and Cook 1984; NIOSH 1977a, 1977d, 1977e, 1977f, 1977g 1977h; Que Hee and Boyle 1988; Que Hee et al. 1985a; Wielopolski et al. 1986). Available methods for determining lead in body fluids are sensitive and reliable for measuring background exposure levels, as well as exposure levels at which health effects have been observed to occur. Blood lead levels have been found to correlate best with exposure concentrations (Rabinowitz et al. 1985). Methods of quantifying lead in tissues, bone, teeth, and hair are generally reliable, but are only sensitive at relatively high exposure concentrations. There is a need for more sensitive methods of detection for matrices so that correlations between lead levels in these media and exposure concentrations can be more reliably determined. Several nonspecific biomarkers are used to assess exposure to lead. These include ALAD activity and ALA, EP, coproporphyrin, and 1,25-dihydroxyvitamin D concentrations (Braithwaite and Brown 1987; EPA 1986a; Grandjean and Olsen 1984; Stokinger 1981; Tabuchi et al. 1989; Tomokuni and Ichiba 1988; Tomokuni et al. 1988). The methods for determining these variables are sensitive, reliable, and well established. No additional research for these biomarkers appears to be needed.

Existing methods for measuring lead in biological fluids and tissues are the same as those for exposure. The limitations and anticipated research needs are the same in that there is a need for improved methods of quantifying lead in tissues, bone, teeth, and hair. The primary biomarkers of effect for lead are ALAD, EP, basophilic stippling and premature erythrocyte hemolysis, and presence of intranuclear lead inclusion bodies in the kidneys. Sensitive, reliable, well-established methods exist to monitor for these biomarkers; however, they are not specific for lead exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Numerous analytical methods are available for measuring inorganic and organic lead compounds in air, water, sediments, soil, fish, agricultural products, and foodstuffs (Eckel and Jacob 1988; EPA 1982a, 1986a, 1988b, 1988f, 1989f, 1989h, 1990c; Lee et al. 1989; Maenhaut et al. 1979; Mielke 1992; Mielke et al. 1983, 1985, 1989). Most of these are sensitive and reliable for determining background concentrations of lead compounds in the environment and levels at which health effects might occur. The most frequently used methods are AAS, GFAAS, ASV, and ICP-AES, the methods recommended by EPA and NIOSH (Birch et al. 1980; EPA 1988b; NIOSH 1977c, 1981, 1984; Scott et al. 1976). The definitive method is IDMS, which is used to produce reference standards by which laboratories can determine the reliability of their analyses (Volkening et al. 1988). No additional analytical methods for determining low levels of lead compounds in environmental media are needed.

6.3.2 On-going Studies

FL Milder (Applied Biomedical Corporation, Massachusetts) is developing a technique using X-ray fluorescence in a transmission geometry to measure total lead, in vivo, noninvasively. The distribution of lead bone stores in cadavers will be investigated and results will be used to design and build a prototype machine for measuring lead in humans. Ultimately, the machine developed will be useful as (1) a diagnostic tool in determining the presence of lead poisoning and elevated levels of body lead; (2) a monitoring device in following the progress of chelation treatment; and (3) a screening device to complement or replace erythrocyte protoporphyrin testing in children and to do epidemiologic studies in adults and children. No additional information concerning methods for measuring lead in biological and environmental samples was located.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding lead in air, water, and other media are summarized in Table 7-1.

ATSDR has not derived an MRL for lead. Neither a reference concentration (RfC) nor a reference dose (RfD) exist for lead and its inorganic compounds because it was decided that no thresholds have been demonstrated for the most sensitive effects in humans. However, EPA (1990a) has determined that the critical effect for lead is central nervous system effects. EPA (1990a) has derived a chronic oral RfD for alkyl leads of 1×10^{-7} mg/kg/day based on liver and neuronal damage in rats (Schepers 1964). A subchronic value of 1×10^{-6} mg/kg/day for the same effect of concern has also been derived, based on the same study. The RfDs based on these chronic and subchronic studies were assigned uncertainty factors of 10,000 and 1,000, respectively.

EPA (IRIS 1990) has assigned lead a weight-of-evidence carcinogen classification of B2, which indicates that lead is a probable human carcinogen. A quantitative estimate of lead carcinogenic risk from oral and inhalation exposure has not been recommended by the Carcinogen Assessment Group. Quantifying lead's cancer risk involves many uncertainties, some of which may be unique to lead. Age, health, nutritional state, body burden, and exposure duration influence the absorption, release, and excretion of lead. Additionally, current knowledge of lead pharmacokinetics indicates that an estimate derived by standard procedures would not truly describe lead's potential risk (IRIS 1990).

The CDC determined in 1991 that blood lead levels of >10 μg/dL were to be considered elevated (CDC 1991).

In an effort to protect human health by reducing the lead levels at consumers' taps to as close to the MCLG (zero) as is feasible, EPA (1989f, 1991a) requires water system authorities to: (1) install or improve corrosion control to minimize lead levels at the tap while ensuring that treatment does not cause the water system to violate any national primary drinking water regulation; (2) install treatment to reduce lead in source water entering the distribution system; (3) replace lead service lines when more than 10% of targeted tap samples exceed 0.015 mg/L lead in drinking water if corrosion control and/or source water treatment does not bring lead levels below the lead action level; and (4) conduct public education programs if lead levels are above the action level.

Lead is regulated by the Clean Water Effluent Guidelines for the following industrial point sources: electroplating, organic and inorganic chemicals, iron and steel manufacturing, nonferrous metals manufacturing, steam electricity, glass manufacturing, asbestos, rubber, timber products processing, metal finishing, mineral mining, ore mining, paving and roofing, paint and ink formulating, gum and wood, carbon black, battery manufacturing, metal molding and casting, porcelain enameling, copper forming, electrical and electronic components, and nonferrous metal forming (EPA 1988b).

The Lead Contamination Control Act of 1988 mandates that the Consumer Product Safety Commission (1) require the repair or recall of drinking water coolers containing lead in parts that come in contact with drinking water, (2) prohibit the sale of drinking water coolers that are not lead-free, (3) require that states establish programs to assist educational agencies in testing and remediating lead contamination of drinking water in schools, and (4) require that EPA certify testing laboratories and provide for coordination by the CDC of grants for additional lead screening and referral programs for children and infants (Congressional Record 1988a, 1988b).

TABLE 7-1. Regulations and Guidelines Applicable to Lead

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification:		IARC 1987
	Lead and inorganic lead compounds	Group 2B[a]	
	Organolead	Group 3[b]	
	Drinking water guidelines	0.050 mg/L	WHO 1984
	Blood lead level of concern	20 µg/dL	WHO 1986
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL TWA (inorganic lead)	0.05 mg/m^3	OSHA 1978 (29 CFR 1910.1025); EPA 1978e
	Action level (8-hour average)	0.03 mg/m^3	OSHA 1978 (29 CFR 1910.1025); EPA 1978e
EPA OAR	No primary lead smelter shall discharge gases with:		
	Particulate matter	>50 mg/dscm	EPA 1976a (40 CFR 60.182); EPA 1976b
	Sulfur dioxide	>0.065%	EPA 1976a (40 CFR 60.183); EPA 1976b
	Opacity	>20%	EPA 1976a (40 CFR 60.184); EPA 1976b
	No secondary lead smelter shall discharge any gases from the following:		EPA 1974a (40 CFR 60.122); EPA 1974b
	Blast or reverberatory furnace with:		
	Particulate matter	>50 mg/dscm	
	Opacity	>20%	
	Pot furnace of >250 kg charging capacity with opacities	>10%	
	Lead-acid battery manufacturing plants shall not discharge gases with the following lead contents:		EPA 1982c (40 CFR 60.372); EPA 1982d
	Gases from grid-casting facilities	>0.40 mg/m^3	
	Paste-mixing facility	>1.0 mg/m^3	
	Three-process operation facility	>1.0 mg/m^3	
	Lead oxide manufacturing facility	>5.0 mg/kg	
	Lead reclamation facility	>4.5 mg/m^3	
	Lead-emitting operation	>1.0 mg/m^3	
	Facilities, not lead-reclamation	>0% opacity	
	Lead reclamation facilities	>5% opacity	
	Levels of lead in gasoline restricted to:		
	Unleaded	0.05 gpg	EPA 1973b (40 CFR 80); EPA 1982b
	Leaded	0.1 gpg	EPA 1973b (40 CFR 80); EPA 1985g
b. Water:			
EPA ODW	Action level in drinking water	0.015 mg/L	EPA 1989f (40 CFR 141, 142); EPA 1991a
	Regulated under SDWA of 1986	Yes	FSTRAC 1988

TABLE 7-1 (Continued)

Agency	Description	Information	References
NATIONAL (Cont.)			
c. Food:			
FDA	FDA action levels:		FDA 1992a
	Leaching solution for pottery flatware	3.0 μg/mL	
	Leaching solution for small hollowware	2.0 μg/mL	
	Leaching solution for large hollowware	1.0 μg/mL	
	Leaching solution for cups and mugs	5.0 μg/mL	
	Leaching solution for pitchers	0.5 μg/mL	
d. Other:			
CPSC	Paint is declared banned from household use and interstate commerce if the lead content exceeds	0.06% total weight of solids or paint film	CPSC 1973 (16 CFR 1500.17); EPA 1973a
EPA OERR	Reportable quantity (proposed):		EPA 1985a (40 CFR 302); EPA 1986b (40 CFR 117); EPA 1992
	Metallic	10 pound	
	Lead acetate	10 pounds	
	Lead chloride	10 pounds	
	Lead fluoroborate	10 pounds	
	Lead fluoride	10 pounds	
	Lead iodide	10 pounds	
	Lead nitrate	10 pounds	
	Lead phosphate	10 pound	
	Lead stearate	10 pounds	
	Lead subacetate	10 pound	
	Lead sulfate	10 pounds	
	Lead sulfide	10 pounds	
	Lead thiocyanate	10 pounds	
	Tetramethyl lead	10 pounds	
EPA OSW	Designated as a hazardous substance for inorganic lead compounds	Yes	EPA 1978b (40 CFR 116.4); EPA 1978a
	Designated as a toxic pollutant under Section 307(a)(1) of the Federal Water Pollution Control Act	Yes	EPA 1979c (40 CFR 401.15); EPA 1979a
	Listing as a hazardous waste: Maximum concentration of contaminants for characteristic of EP toxicity	5 mg/L	EPA 1980b (40 CFR 261.24); EPA 1980c
	Listing as a hazardous constituent	Yes	EPA 1988d (40 CFR 261, Appendix VIII); EPA 1988e
	Groundwater monitoring requirement	Yes	EPA 1987a (40 CFR 264, Appendix IX); EPA 1987b
EPA OTS	Toxic chemical release reporting; Community right-to-know	Yes	EPA 1988g (40 CFR 372); EPA 1987e
HUD	Requires testing and elimination of lead-based paint in federally funded housing and housing rehabilitation programs, public housing, and Indian housing	Yes	HUD 1987a, 1987b

TABLE 7-1 (Continued)

Agency	Description	Information	References
NATIONAL (Cont.)			
HUD	Action level for lead-based paint	1 mg/m^3 (XRF) or 1 mg/cm^2 (AAS or ICP-AES)	HUD 1987a, 1987b
Guidelines:			
a. Air:			
ACGIH	TLV TWA		ACGIH 1990
	Inorganic lead, dust and fumes	0.15 mg/m^3	
	Lead arsenate	0.15 mg/m^3	
	Lead chromate	0.05 mg/m^3	
EPA	RfC (Inhalation)	No data[c]	IRIS 1990
	End point	CNS effects	
NIOSH	REL	<0.1 mg/m^3	NIOSH 1992
OAQPS	NAAQS	1.5 $\mu g/m^3$	EPA 1987c (40 CFR 50.12); EPA 1978d
b. Water:			
EPA ODW	MCLG	0 mg/L	EPA 1989f (40 CFR 141, 142); EPA 1991a
	Health Advisories	No data	IRIS 1990
EPA OWRS	Ambient Water Quality Criteria for Protection of Human Health	50 µg/L	EPA 1980d
	Ambient Water Quality Criteria for Protection of Aquatic Organisms		EPA 1985h
	Freshwater:		
	Acute (1-hour average)	82 µg/L	
	Chronic (4-day average)	3.2 µg/L	
	Marine		
	Acute (1-hour average)	140 µg/L	
	Chronic (4-day average)	5.6 µg/L	
NAS	ADI		HSDB 1990
	Adults	3 mg/wk	
	Children	<3 mg/wk	
c. Other:			
ACGIH	Biological Exposure Indices		ACGIH 1990
	In blood	50 µg/dL	
	In urine	150 µg/g creatinine	
CDC	Blood lead level of concern in children	10 µg/dL	CDC 1991
OSHA	Blood lead level of concern	40 µg/100 g (of whole blood)	OSHA 1978 (29 CFR 1910.1025); EPA 1978e

TABLE 7-1 (Continued)

Agency	Description	Information	References
NATIONAL (Cont.)			
EPA	RfD (oral) (metallic)	No data[d]	IRIS 1990
	End point	CNS effects	
	Alkyl leads:		EPA 1990a
	Chronic	1.00×10^{-7} mg/kg/day (u.f. 10,000)	
	End point	Liver and neuronal	
	Subchronic	1.00×10^{-6} mg/kg/day (u.f. 1,000)	
	End point	Liver and neuronal	
	Carcinogen classification	Group B2	IRIS 1990
	Unit risk (inhalation)	No data	EPA 1990a
	Unit risk (oral)	No data	EPA 1990a
STATE			
Regulations and Guidelines:			
a. Air:			
	Acceptable ambient air concentrations		NATICH 1990
California-Monterey		0.00	
Connecticut	(8-hour)	3.00 $\mu g/m^3$	
Kansas-Kansas City	(1-year)	0.357 $\mu g/m^3$	
Kansas	(Annual)	0.357 $\mu g/m^3$	
Massachusetts	(24-hour)	0.140 $\mu g/m^3$	
Massachusetts	(Annual)	0.070 $\mu g/m^3$	
Maryland		0.00	
Maine		0.00	
North Dakota	(8-hour)	0.0015 mg/m^3	
Nevada	(8-hour)	0.004 mg/m^3	
Pennsylvania-Philadelphia	(1-year)	1.50 $\mu g/m^3$	
Pennsylvania-Philadelphia	(Annual)	1.50 $\mu g/m^3$	
Virginia	(24-hour)	2.50 $\mu g/m^3$	
Vermont	(3-month)	1.50 $\mu g/m^3$	
	Designated as a hazardous air pollutant and subject to regulations		CELDS 1990b
Iowa		Yes	
Montana		Yes	
Utah		Yes	
	Ambient air emissions limitations for Class I areas		CELDS 1990a
Kentucky	(3-month)	0.1 $\mu g/m^3$	
Montana	(24-hour)	0.1 $\mu g/m^3$	
	Permit required to construct and operate an air contamination source project if yearly emissions exceed:		CELDS 1990a
Arizona		0.6 ton	
Connecticut		0.6 ton	
Missouri		0.6 ton	

TABLE 7-1 (Continued)

Agency	Description	Information	References
STATE (Cont.)			
New York		0.6 ton	
Virginia		0.6 ton	
	Prevention of significant deterioration: Sources exempt from air monitoring requirements if net emissions increase is:		CELDS 1990a
Delaware	(24-hour average)	$<0.1 \mu g/m^3$	
Louisiana	(24-hour average)	$<0.1 \mu g/m^3$	
Oregon	(24-hour average)	$<0.1 \mu g/m^3$	
Wisconsin	(24-hour average)	$<0.1 \mu g/m^3$	
b. Water:			
	Drinking water quality guidelines and standards		FSTRAC 1988
Maine		20 µg/L	
Minnesota		20 µg/L	
	MCL in drinking water		
Alabama		0.02 mg/L	CELDS 1990a
Iowa		0.05 µg/L	CELDS 1990b
Texas		0.05 mg/L	CELDS 1990a
Arizona	Permit requirement for operation of stationary source emitting	>5 tons/year	CELDS 1990a
California	Toxic materials limitations objectives for protection of marine aquatic wildlife		CELDS 1990b
	6-month median	2 µg/L	
	Daily maximum	8 µg/L	
	Instantaneous maximum	20 µg/L	
Iowa	Surface water quality criteria		IAC 1986a
	Class B waters[e]	0.1 mg/L	
	Class C waters[f]	0.05 mg/L	
Illinois	Water quality standards		IEPA 1988a
	General use	100 µg	
	Public and food processing water supply	50 µg	
	Lake Michigan	50 µg	
	Secondary contact and indigenous aquatic life	100 µg	
	General effluent standards	0.2 mg/L	IEPA 1988b
Indiana	Constituent comprising groundwater protection standards	Yes	CELDS 1990b
Kentucky	Domestic water supply source criteria	0.05 mg/L	NREPC 1987 (401 KAR 5:031)
	Maximum groundwater contaminant level	0.05 mg/L	NREPC 1988 (401 KAR 30:020)
	Significant emission levels of toxic air pollution	3.83×10^{-5} pounds/hour	NREPC 1986 (401 KAR 63:021)
	Interim primary drinking water standards	0.05 mg/L	NREPC 1988 (401 KAR 35:310)

TABLE 7-1 (Continued)

Agency	Description	Information	References
STATE (Cont.)			
New York	Effluent standards: Maximum allowable concentrations into saturated or unsaturated zones	0.05 mg/L	CELDS 1990a
	Allowable concentration limits for Class GA waters	0.025 mg/L	CELDS 1990a
Nevada	Water quality criteria		CELDS 1990b
	Irrigation	<5.0mg/L	
	Watering of livestock	<0.1mg/L	
	Propagation of wildlife	<0.1mg/L	
	Municipal or domestic water supply	0.05 mg/L	
	Ground water standards		
New Mexico		0.05 mg/L	CELDS 1990b
Utah		0.05 mg/L	CELDS 1990a
Wisconsin	Public health groundwater quality standards:		WAC 1985
	Enforcement standard	50 µg/L	
	Preventative action limit	5 µg/L	
c. Other:			
California	Chemical parameter for leachate monitoring	Yes	CELDS 1990b
Iowa	Land application of sludge and solid waste from publicly owned treatment center: No permit required if lead level does not exceed	1,000 mg/kg	IAC 1986b
Kentucky	Defined as hazardous waste	Yes	NREPC 1988 (401 KAR 31:040)

[a]Group 2B: Possible Human Carcinogen
[b]Group 3: Not classifiable as to their carcinogenicity to humans
[c]Final Draft of Air Quality Criteria Document (600/8-83-028F) declines to derive an air quality criterion for lead.
[d]Not verified by the CRAVE workgroup and further discussion not scheduled
[e]Protected for wildlife, fish, aquatic and semiaquatic life and secondary contact water uses
[f]Protected as a raw water source of potable water supply

AAS = atomic absorption spectroscopy; ACGIH = American Conference of Governmental Industrial Hygienists; ADI = Acceptable Daily Intake; CDC = Centers for Disease Control; CNS = central nervous system; CPSC = Consumer Product Safety Commission; dL = deciliter; dscm = dry standard cubic meter; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; gpg = grams per gallon; HUD = Department of Housing and Urban Development; IARC = International Agency for Research on Cancer; ICP-AES = Inductively Coupled Plasma-Atomic Emission Spectroscopy; MCL = Maximum Contaminant Level; MCLG = Maximum Contaminant Level Goal; NAAQS = National Ambient Air Quality Standard; NAS = National Academy of Sciences; NIOSH = National Institute for Occupational Safety and Health; OAQPS = Office of Air Quality Planning and Standards; ODW = Office of Drinking Water; OAR = Office of Air and Radiation; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; REL = Recommended Exposure Limit; RfC = Reference Concentration; RfD = Reference Dose; SDWA = Safe Drinking Water Act; TLV = Threshold Limit Value; TWA = Time-Weighted Average; XRF = X-Ray Fluorescence

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo -- Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50}) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text.

The legends presented below demonstrate the application of these tables and figures. A representative example of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1). Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes.

(2). Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

(3). Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.

(4). Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-1).

(5). Species The test species, whether animal or human, are identified in this column.

(6). Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

(7). System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.

(8). NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9). LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

(10). Reference The complete reference citation is given in Chapter 8 of the profile.

(11). CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.

(12). Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See LSE Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure levels for particular exposure duration.

(13). Exposure Duration The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14). Health Effect These are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.

(15). Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16). NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17). CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

(18). Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1^*).

(19). Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation

Key to figure[a]	Species	Exposure frequency/duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
3 → Systemic	5	6	7	8	9		10
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer						11	
38	Rat	18 mo 5d/wk 7hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

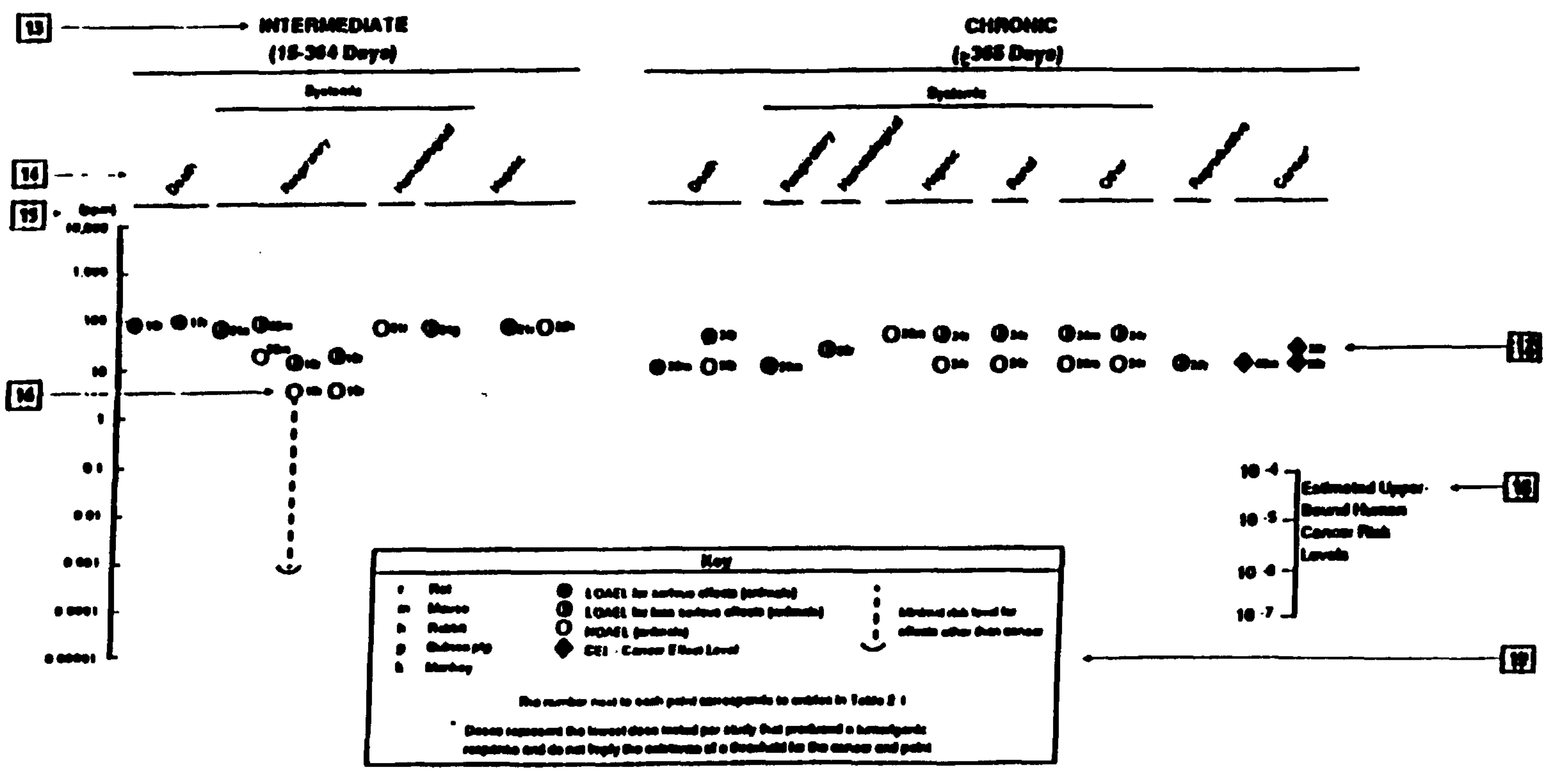

FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, - chronic). These MRLs are not meant to support regulatory action, but to aquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" and 2.7, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
dL	deciliter
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient

L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

APPENDIX C

PEER REVIEW

A peer review panel was assembled for lead. The panel consisted of the following members: Dr. Deborah Cory-Slechta, Associate Professor of Toxicology and Pediatrics, Environmental Health Science Center, University of Rochester, Rochester, New York; Dr. Joseph P. Gould, Research Scientist, School of Civil Engineering, Georgia Institute of Technology, Atlanta, Georgia; Dr. Shane Que Hee, Associate Professor, Department of Environmental Health Sciences, UCLA School of Public Health, Los Angeles, California; Dr. Alan Hall, Private Consultant, Evergreen, Colorado; Dr. Edward Morgan, Assistant Professor, Department of Pharmacology, Emory University, Atlanta, Georgia; and Dr. Peter Lacouture, Associate Director, Clinical Research, The Purdue Frederick Company, Norwalk, Connecticut. These experts collectively have knowledge of lead's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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